Symposium on Parenteral Fluids, Nutrition and Electrolytes

March 5-6, 1954

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This symposium, sponsored by the Hennepin County Medical Society and the Academy of General Practitioners, was suggested by Dr. Robert Herwick, medical director of the Baxter Laboratories, to Dr. Carl O. Rice who was responsible for its organization.

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The Milliequivalent as a Unit of Measure in the Interpretation and Correction of Electrolyte Disturbances

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A FEW YEARS ago after almost every medical lecture, there was at least one person in the audience who would rise and ask the speaker what the pH of the solution was. As he settled himself comfortably in his chair, one could observe a satisfied expression on his face which indicated that he felt he had impressed both the speaker and the audience with his erudition. Now pH is commonly used and has been accepted as the most convenient and simplest way to express hydrogen ion concentration in biological systems.

Although the term "milliequivalent" probably could also be used nowadays to impress the uninitiated, its chief value lies in the fact that the application of chemical equivalence to the measurement of electrolytes simplifies the diagnosis and treatment of disturbance in electrolyte and fluid balance.

Before defining the term "milliequivalent," it would probably be best first to explain the meaning of chemical equivalence. If the weight in grams of NaOH, KOH, and HCl corresponding to the molecular weight of these substances has been dissolved in enough water to make one liter, each solution will contain, respectively, 40 gm. of NaOH, 56 gm. of KOH, and 37 gm. of HCl *(i.e.,* molecular weight of hydrogen = 1, chloride = 36, and HCl = 37). These are called molar solutions, and they contain one mole of the substance per liter. "When equal volumes are mixed (for example, 1 cc. of the alkaline NaOH solution and 1 cc. of the acid HCl solution), they neutralize each other. The same result is obtained when 1 cc. of alkaline KOH solution is mixed with 1 cc. of the HCl solution. The two alkaline solutions show the same combining power or the same activity for equal volumes. Each contains the same number of active particles per unit volume, but the weights of the substances per unit volume are not the same. Since one mole of NaOH exhibits the same combining power as one mole of KOH, they are equivalent, mole for mole. Hence, one equivalent of any of the three substances is one mole of the substance. It is evident that the comparison of two alkalies in terms of their equivalence brings us much closer to what we want to know about their presence in living systems than does the comparison in terms of weight."[1]

Substances react also on the basis of their valence. The chemicals mentioned thus far are all univalent. But calcium (atomic weight = 40) is bivalent; that is, one mole of Ca, which is 40 gm., possesses twice the combining power of one mole of Na. Hence, one mole of Ca is two equivalents of Ca, and one equivalent of Ca weighs 20 gm.

Since the concentration of electrolytes in the blood is relatively low, it is easier to express the values in whole numbers by using as a unit of measure 1/1,000 of an equivalent, or milliequivalent.

The average concentration of each electrolyte expressed in terms of milliequivalents is shown on left side of Table I.

Under normal conditions the extracellular fluid (the plasma plus the fluid that surrounds the cells — the interstitial fluid) contains approximately 155 milliequivalents per liter of cations (base ions which have a positive electrical charge) and an equal number of anions (acid ions which bear a negative charge).

All of the components except protein are readily diffusible into the interstitial fluid, so that, with the exception of protein, the concentration of these

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TABLE I.

ELECTROLYTE COMPOSITION OF BLOOD PLASMA

(Cations) + mEq./liter		(Anions) − mEq./liter		(Cations) + mg./100 cc.		(Anions) −	
		HCO_3	27			HCO_3	60 vols. %
		Cl	103			Cl	365 mg. %
Na	142	HPO_4	2	Na	327	HPO_4	3.5 mg. %
K	5	SO_4	1	K	20	SO_4	1.5 mg. %
Ca	5	Org. Acids	6	Ca	10	Org. Acids	
Mg	3	Protein	16	Mg	3.6	Protein	7 gm./100 cc.
	155		155				

$HCO_3 + Cl = 27 + 103 = 130$
$Na = 142$ therefore $142 - 130 = 12$
Therefore $HCO_3 + Cl + 12 =$ Na concentration

ions in the fluid surrounding the cells is essentially the same as that in the plasma. This table also illustrates the advantages of expressing the concentration of all components in the same unit, so that the total concentration of cations and anions can be obtained. This is the main advantage of the system based on chemical equivalence. The total concentration of cations always equals that of the anions in all fluids.

On the right side of Table I is shown the values of electrolytes expressed in the terms used before the introduction of milliequivalents. Note that 3 different units are used: mg. per cent, volumes per cent, and grams per 100 ml. Chloride is sometimes even expressed as mg. of NaCl per ml. of plasma. It is difficult to compare the biological relationships of the different components of plasma under these conditions.

At the bottom of Table I is shown the relationship of the carbon dioxide content and chloride concentration to the sodium concentration of the plasma when expressed in milliequivalents per liter. The sum of values for bicarbonate and chloride ions normally is about 130 mEq. The difference between this value and the concentration of sodium is 12 mEq./liter. Consequently in the absence of an abnormal accumulation of other anions, the sum of the bicarbonate and chloride ion plus 12 is an approximation of the sodium concentration.

When laboratory facilities are not available for sodium and potassium analysis, this calculation is often a valuable means of estimation of the sodium concentration of plasma.

The application of this calculation in estimating the sodium concentration in the plasma of surgical patients in electrolyte imbalance is shown in following examples. On the left is shown the actual analysis. On the right the estimated sodium concentration.

Example 1

Determined Values			Calculation
$Na+$	=	121 mEq./L.	$20.8 + 84.3 = 105$
$K+$	=	4.5 mEq./L.	$105 + 12 = 117$ mEq. of
Cl^-	=	84.3 mEq./L.	Na.
HCO_3^-	=	20.8 mEq./L.	

Example 2

Determined Values			Calculation
$Na+$	=	123 mEq./L.	$27.2 + 84.1 = 111.3$
$K+$	=	2.8 mEq./L.	$111 + 12 = 123$ mEq. of
HCO_3^-	=	27.2 mEq./L.	Na.
Cl^-	=	84.1 mEq./L.	

In the second example, the normal CO_2 content with the low chloride value yields additional information. As Darrow pointed out, a high CO_2 content compared to the chloride content is often a sign of intracellular potassium deficiency. In this plasma, a low K value was found by analysis with a flame photometer.

Conversion of Milligrams Per Cent to Milliequivalents Per Liter

Values expressed as milligrams per 100 ml. can be converted to milliequivalents per liter by using the following formula:

$$\frac{\text{mg. per 100 ml.} \times 10}{\text{atomic weight}} \times \text{valence} = \text{mEq./L.}$$

Example: 360 mg./100 ml. chloride $= \frac{360 \times 10}{35} \times 1$

$= 103$ mEq./L.

In the case of gases (e.g., carbon dioxide), advantage is taken of the fact that a quantity of gas equal in weight to its molecular weight in grams occupies 22.4 liters under standard conditions. The formula used is:

$$\text{mEq./L.} = \frac{\text{vol. \%} \times 10}{22.4}$$

Example: CO_2 of 60.5 vol. % $= \frac{60.5 \times 10}{22.4} = 27$ mEq./L.

Factors which simplify these conversions are given in Table II.

The usefulness of milliequivalents in planning the treatment of electrolyte and fluid imbalance is illustrated by the following example:

Calculation of Theoretical Electrolyte Deficit

Example: A patient weighing 132 pounds is found to have a concentration of 128 mEq./L. of sodium in the plasma. How much sodium chloride

is needed to replace the deficit? The amount of sodium chloride needed to replenish the extracellular deficit of sodium can be estimated as follows: To convert pounds to kilograms, divide the patient's weight by 2.2. Therefore $\frac{132}{2.2} =$ 60 Kg.

The average normal concentration of sodium (Table I) is 142 mEq./L. The patient's plasma level for this ion is 128 mEq./L. Substituting in the following formula:

Amount of ion needed (in mEq.) = volume of extracellular fluid (1/5 body weight) X (normal value of ion mEq./L. - patient's value mEq./L.).

Example: $\frac{60}{5}$ X (142 - 128) = 168 mEq. of sodium needed.

It is seen from Table III that this calculated deficit of sodium is supplied by 1,090 milliliters of isotonic saline, 190 milliliters of 5 per cent sodium chloride, etc.

As many authors have pointed out, calculation of sodium deficit on the basis of 20 per cent of the body weight results in a quantity much lower than the actual needs for replacement, apparently because of replenishment of intracellular deficit. Some authors prefer to make such calculations on total body water, using 60 per cent of ideal body weight (in kilograms).

In addition to expressing plasma electrolyte concentrations in milliequivalents, it is also advantageous to express the concentration of repair solutions in the same unit. In chart III, for example, if one compares the concentration of the salts in Ringer's solution in terms of grams with milliequivalents per liter, it is obvious how much easier it is to relate the amount of individual ions in the repair solutions to the deficit in tissue electrolytes to be corrected.

It can be seen, then, that the milliequivalent as a unit of measure simplifies and facilitates the interpretation and correction of electrolyte disturbances.

TABLE II. DATA FOR CONVERSION OF SERUM (OR PLASMA) ELECTROLYTES TO mEq./LITER

Electrolyte	Calculated As:	Valence	Equiv. Weight	Conversion Factor	
				Multiply By	Divide By
Sodium	Sodium	1	23	0.434	2.3
Potassium	Potassium	1	39	0.256	3.9
Calcium	Total Ca	2	20	0.500	2
Magnesium	Magnesium	2	12	0.833	1.2
Bicarbonate	CO_2 capacity	—	22.4*	0.446	2.2
Chloride	Chloride	1	35.5	0.281	3.5
	NaCl	1	58.5	0.170	5.8
Phosphate inorganic	Phosphorus	1.8	17.2	0.580	1.7
Sulfate inorganic	Sulfur	2	16	0.625	1.6
Protein	Protein	—	—	2.43	

*22.4 liters per mole.

TABLE III. ELECTROLYTE CONCENTRATIONS OF SEVERAL COMMONLY USED PARENTERAL FLUIDS

Solution	Gm./L.	mEq./L. Cations	mEq./L. Anions
Isotonic saline (0.9% NaCl)	9.0	154 Na	154 Cl
Hypotonic saline (0.45% NaCl)	4.5	77 Na	77 Cl
Hypertonic saline (5.0% NaCl)	50.0	850 Na	850 Cl
Ringer's Solution (Isotonic Solution of Three Chlorides)	8.6 NaCl 0.3 KCl 0.33 $CaCl_2$	147 Na 4 K 6 Ca	157 Cl
One-Sixth Molar Lactate (molar solution diluted to 1/6)	18.66 Na Lact.	166 Na	166 mM. lactate
Sodium bicarbonate (1.5%)	15.0 $NaHCO_3$	178 Na	178 mM. bicarbonate
Ringer's Lactate	6.0 NaCl 0.3 KCl 0.2 $CaCl_2$ 3.1 Na Lact.	130 Na 4 K 4 Ca	111 Cl 27 mM. lactate

Reference

1. Newburgh, L. H.: The Significance of Body Fluids in Clinical Medicine, Springfield, Illinois: Charles C Thomas, 1950.

Relation of Alkalosis to Potassium Deficiency

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FOR THE past ten years, I have been studying the relation of alkalosis to loss of body potassium. The recent work which seems to clarify the pathogenesis of alkalosis has been carried out together with Robert E. Cooke and a group of students—Martin Vita, Saul Brusilow, Claude Reed and Donnel Etzwiler—who did various parts of the study as their theses. I shall not apologize for discussing more of the physiology of body fluids than the therapeutic practice. As you all know, therapy cannot be designed to meet individual problems without understanding the physiologic disturbance which one is trying to correct.

As long as it was thought that alkalosis did not involve changes in the composition of the cells and changes in renal function, it was rational to treat alkalosis with physiologic saline alone. We now know that alkalosis is frequently, if not invariably, accompanied by low K and high intracellular Na in the muscles. The work which I shall discuss shows certain changes in renal function which accompany K deficiency. These studies demonstrate that K as well as NaCl is necessary in the treatment of most cases of alkalosis.

Table I shows the data obtained on rats receiving a diet practically devoid of Na, K and Cl, together with drinking water having the contents of Na, Cl and K shown in the table. The rats received these solutions and the diet for fourteen to twenty-one days and were then killed. This procedure gave a large load of $NaHCO_3$ and variable amounts of K and Cl. Your attention is first directed to the serum concentrations and the muscle contents per 100 gm of fat free solids. It is notable that alkalosis did not develop except when muscle K became low and intracellular Na high. The first two groups show that alkalosis did not develop in response to the large load of $NaHCO_3$ as long as 5 mm. or more of KCL per liter was present in the drinking solution. The next two groups show that alkalosis developed when the solution contained 3 mm. or less of KCL per liter. However, alkalosis developed in

TABLE I.

15 - 20 Day $NaHCO_3$ Loads

	Drinking Water			Serum		Muscle	
	HCO_3	K	Cl	HCO_3	Cl	K	Na_i
1)	150	10	10	24	101	-	-
2)	150	5	5	25	100	43	4.6
3)	150	3	5	34	87	35	10.5
4)	150	1.5	5	34	88	-	-
5)	150	5.0	1.5	30	88	41	9.7
6)	150	1.5	15	31	88	39	10.3
7)	30	1	1	30	95	39	7.2
8)	150	15	1.5	25	98	43	4.9

Concentrations in mEq per L for serum and drinking water, and per 100 gm fat-free solids for muscle. HCO_3 is presented as Na HCO_3. Na is calculated intracellular Na.

Group fivewhen Cl was 1.5 mEq, and K, 5 mEq per L. Thus, 5 mEq of K did not prevent alkalosis when Cl intake was very low. In Group seven the characteristic changes of alkalosis developed when the load of $NaHCO_3$ and K and Cl were reduced in proportion. For this reason, one may conclude that minimum intakes of K and Cl are necessary to protect from alkalosis even with a reduced load of $NaHCO_3$. Group eight shows that a higher intake of K prevents alkalosis when the Cl intake is the same as in Group five. As a whole the experiments demonstrate that K and Cl are necessary to prevent alkalosis when a large load of $NaHCO_3$ is given.

When the intake of K per Kg per day is related to serum bicarbonate concentration, it was found that alkalosis did not develop as long as 0.4 mEq of K per Kg per day was ingested. Chart I shows that when the intake of K was 0.4 mEq, alkalosis

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developed if the intake of Cl was less than 0.4 mEq per Kg per day.

The next group of experiments shows the change in serum and muscle composition of rats

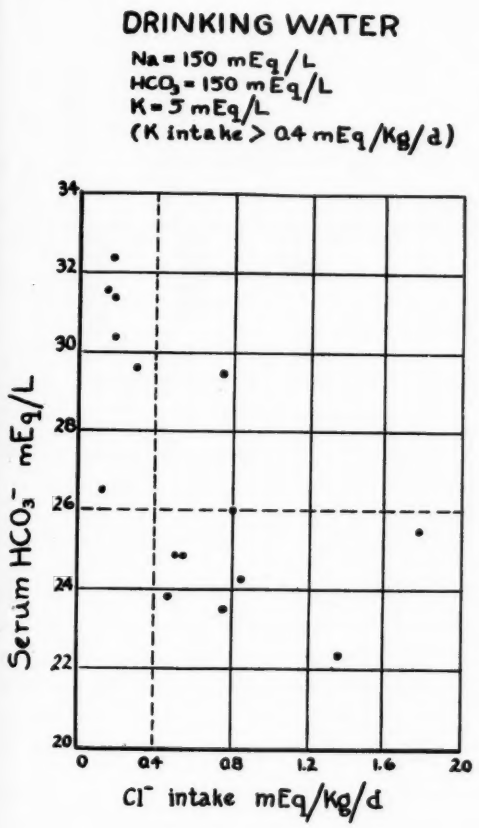

Chart I

receiving a single intraperitoneal injection of 15 mEq of $NaHCO_3$ per Kg. The analyses were made twelve hours later. The results in normal rats and rats with K deficiency produced by injection of desoxycorticosterone acetate while fed a diet low in K are shown in Table II. The normal rats are shown in the top two rows, and the K deficient rats in the last two rows.

Despite the large dose of $NaHCO_3$, the normal rats did not develop alkalosis of the serum but about 6 mEq of K were lost from the muscle and intracellular Na increased about 4 mEq. These values represent approximately the muscle changes in a Kg of rat. The normal rats excreted about 60 per cent of the $NaHCO_3$ and 90 per cent of the water. Cation excretion was about equivalent to dose of 15 mEq of $NaHCO_3$, but 9 mEq was Na and 6, K. The excretion of Na and the exchange of intracellular K for Na explains the failure to develop extracellular alkalosis.

TABLE II. SERUM CONCENTRATIONS IN MEQ PER L. MUSCLE PER 100 *g*M. FAT-FREE SOLIDS.

Serum and Muscle Composition After 15 mM/Kg of $NaHCO_3$ I.P.

Group	Serum			Muscle		
	Cl	HCO_3	K	Cl	K	Na_i
Normal						
0 h.	100	25	4.5	5.5	46	3
12 h.	99	25	3.6	6.4	40	7.4
K Deficient						
0 h.	90	28	2.3	5.8	33	12.2
12 h.	78	42	2.4	5.2	33	12.4

TABLE III. SERUM CONCENTRATIONS MEQ PER L.

Average Serum Concentrations
Treated Animals Received 3 mM/Kg of $KHCO_3$ b.i.d.

Group	No.	Days	Na	K	Cl	HCO_3
Normal			143	5.0	100	24
K deficient	4	0	142	2.2	84	33
$KHCO_3$ 6 mM	4	1	145	3.1	91	34
$KHCO_3$ 12 mM	4	2	143	3.7	93	28
$KHCO_3$ 18 mM	4	3	143	4.0	99	27
$KHCO_3$ 24 mM	8	4	142	4.2	97	26
Completely Corrected Animals						
$KHCO_3$ 24 mM	5	4	142	4.5	101	23.5

Practically no Cl was excreted by these rats.

The rats deficient in K excreted only about 40 per cent of the $NaHCO_3$; the serums showed marked alkalosis but the muscles did not undergo further changes. Appreciable amounts of Cl were excreted but practically no K. These experiments illustrate the two mechanisms of defense against alkalosis: first, the ability of the rats to excrete Na in excess of Cl which is impaired when K is not available and second, the exchange of intracellular K for extracellular Na which requires normal cellular composition to be effective.

In previous experiments, alkalosis with K deficiency was corrected by administering 6 mM of KCl per Kg per day. It was shown that the exchange of the administered KCl between extracel-

lular and intracellular fluids of muscle corrected the alkalosis without intervention of the kidneys. In effect, 3 K exchanged for 2 Na in the muscles. This left extracellular fluids with 2 NaCl and one Cl and one H. The H and Cl reacted with $NaHCO_2$ to form one NaCl. Table III shows similar experiments in which 6 mM of $KHCO_3$ were injected each day into rats with alkalosis and K deficiency. The exchange in the muscle is essentially the same; 3 K exchanges for 2 Na. Extracellular fluids are left with 2 $NaHCO_3$ and one H and one HCO_3. Treatment with $KHCO_3$ cannot correct alkalosis without excretion of Na in excess of Cl.

TABLE IV. MUSCLE CONTENTS PER 100 GM. FAT-FREE SOLIDS.

Average Muscle Composition Per 100 Gms. Fat-Free Solids Treated Animals Received 3 mM/Kg of $KHCO_3$ b. i. d.

Group	No.	H_2O	Cl	Na	K	Na_i
Normal		340	5.5	10.0	46	3
K deficient	4	323	5.0	19.5	28.8	15
$KHCO_3$ 6 mM/Kg	4	326	5.0	16.0	35.8	9.5
$KHCO_3$ 12 mM/Kg	4	326	5.0	13.5	38.0	7.8
$KHCO_3$ 18 mM/Kg	4	325	5.1	13.0	40.0	7.5
$KHCO_3$ 24 mM/Kg	8	317	5.0	11.8	41.3	6.5
Completely Corrected Animals						
$KHCO_3$ 24 mM/Kg	5	320	5.0	10	43.5	4.5

Tables III and IV show the gradual correction of extracellular alkalosis and muscle composition. In four days, five of eight rats showed essentially normal composition of both serums and muscle. A decrease of about 10 per cent in body weight indicated a loss of body water.

Chart II shows the balances based on urinary excretion and the injected $KHCO_3$. Almost all the administered K was retained during the first two days but practically all the injected K was excreted during the fourth day. Accompanying the retention of K, Na was excreted but the urines were practically free of Cl. Other data which will not be presented show that the excretion of an excess of cations over fixed anions was accomplished with little or no change in urinary pH since urinary organic acids were increased. In rats, at least, an excess of cations may be excreted by substitution of organic acids for Cl just as an excess of anions are excreted in acidosis without a great change in pH by the substitution of NH_4 for Na and K.

The balance data predict the changes in serum and muscle composition within the accuracy of the methods. Wallace and associates showed that total body Cl was unchanged in alkalosis with K deficiency despite low chloride in the serum. For this reason, extracellular fluids are apparently expanded in this type of alkalosis. Thus Cl retention is not necessary for recovery of Cl concentration in rats having alkalosis with K deficiency. The rise in serum concentration of Cl during administration of $KHCO_3$ is explained by the decrease in body water leading to a decrease in extracellular volume. The correction of this type of alkalosis, therefore, involves not only a control of extracellular concentrations but a regulation of extracellular volume.

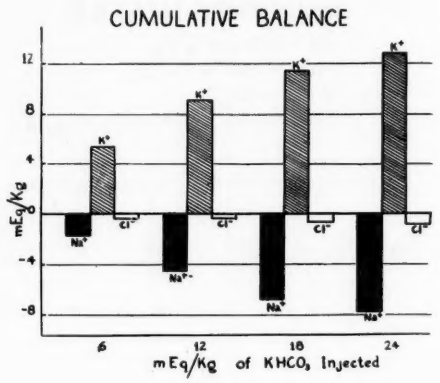

Chart II.

Renal function is usually described in terms of excretion. However, since about 180 liters of glomerular filtrate is formed each day in the average adult, about fourteen times the extracellular contents of water, Na and Cl pass through the glomeruli each day. Since only one to two liters of water and a very small fraction of the filtered Na and Cl are excreted in the urine each day, most of the glomerular filtrate is returned to the body. Consideration of the quantities involved shows that extracellular composition is preserved by reabsorbing Na and Cl from the glomerular filtrate at the concentrations that are maintained. This is the mechanism which preserves body composition. For this reason renal function is best described in terms of the overall composition of the fluid reabsorbed from the glomerular filtrate. If normal extracellular composition is maintained the concentration of the fluid reabsorbed must be approximately the same as that of a glomerular

filtrate, namely, Na 140 and Cl 114 mEq per liter. If alkalosis is maintained the fluid reabsorbed must be low in Cl relative to Na and have the composition that the body tends to maintain.

TABLE V.

Glomerular Filtrate and Reabsorbate Normal

	Concentrations		Amounts	
	Filtr.	Reabsorb.	Reabsorbed	Excreted
Cl mM	110	110	110	0
Na mM	140	140	140	0
H_2O gm	1000	1000	1000	0

The implications of these concepts are illustrated in Tables V, VI and VII. On the left, the concentration of the glomerular filtrate and of the fluid reabsorbed are shown. To the right the maximum possible reabsorption from a liter of glomerular filtrate is shown together with the consequent balance of water, Na and Cl.

Table V demonstrates that all the water, Na and Cl can theoretically be absorbed when normal composition is maintained by absorption at the same concentration as the filtrate. Table VI shows the change in the fluid reabsorbed when alkalosis develops and is maintained as a result of K deficiency. All the water and Na may theoretically be reabsorbed from a glomerular filtrate of normal composition if the fluid reabsorbed has the composition which will be maintained in alkalosis. However, some Cl must be excreted. In Table VII the recovery from alkalosis is shown. In this case all the Cl may be reabsorbed, but part of the water and Na must be excreted. The change in the fluid reabsorbed is probably gradual but the direction of the changes are correctly indicated by the tables. It will be seen that if a load of NaCl is given during K deficiency, the tendency to reabsorb Na and water in excess of Cl will tend to expand extracellular fluids. During recovery from alkalosis, the tendency to reabsorb only part of the water and Na will tend to contract extracellular fluids unless a high intake of NaCl overcomes this tendency. Thus, consideration of the control of extracellular concentrations in terms of the composition of the fluid reabsorbed shows that this process also explains the expansion of extracellular fluids during development of alkalosis and the contraction during recovery.

What, then, are the practical therapeutic implications of these studies? I am sure that alkalosis

TABLE VI.

Glomerular Filtrate and Reabsorbate Development of K Deficiency Alkalosis*

	Concentrations		Amounts	
	Filtr.	Reabsorb.	Reabsorbed	Excreted
Cl mM	110	100	100	10
Na mM	140	140	140	0
H_2O gm	1000	1000	1000	0

*The table applies equally well to the compensated respiratory acidosis.

TABLE VII.

Glomerular Filtrate and Reabsorbate Recovery from K Deficiency Alkalosis

	Concentrations		Amounts	
	Filtr.	Reabsorb.	Reabsorbed	Excreted
Cl mM	100	110	100	0
Na mM	140	140	128	12
H_2O gm	1000	1000	910	90

can develop without K deficiency. We have shown, however, that otherwise normal experimental rats do not develop alkalosis except when renal function is impaired by deficit of water. As long as renal function is relatively normal and body water has been maintained, alkalosis is apparently accompanied by some degree of K deficiency. Furthermore, as long as K deficiency persists, the kidneys maintain alkalosis owing to the change in renal function shown in the experiments which have been discussed. For this reason the treatment of alkalosis should practically always include the administration of KCL as well as NaCl. KCl is essential as long as food cannot be taken. The cure of alkalosis with K deficiency by NaCl alone is only apparent since food contains abundant K. The use of NH_4Cl is contraindicated since the changes in body composition show that the deficit of base in the cells is greater than the deficiency of Cl in extracellular fluids. The body suffers from acidosis of the cells which is greater than the alkalosis of extracellular

fluids. NH_4Cl can only aggravate the cellular acidosis while temporarily restoring extracellular bicarbonate.

The amount of NaCl required is variable. If Na concentration is low, about 60 ml per Kg of physiologic saline in adults and perhaps 80 ml in infants is indicated. However, if serum Na concentration is normal, 20 to 40 ml per Kg should suffice.

The deficit of K is likely to be at least 6 mEq per Kg and may be as great as 17 mEq per Kg. Owing to the dangers of too rapid administration of K, the deficit of K cannot be rapidly replaced and usually requires four to six days of K therapy for complete correction.

Administration of K requires two considerations: (1) the normal rate of expenditure when all fluids are given parenterally. This is 1 to 2 mEq per 100 calories metabolized or 1 to 2 mEq of each 125 to 150 ml of fluid administered to maintain body water; (2) sufficient additional K must be given to assure K retention. It is safe to administer 3 mEq of KCl per Kg of body weight per day if renal function is normal and a cellular deficit of K is present. More than this amount of K may be given if it is known that serum K remains low or if electrocardiogram shows the changes characteristic of low serum K concentrations. The rule is to inject the estimated dose of K for twenty-four hours over a period permitting equal distribution in body fluids. If the total dose is given over a period of four hours, equal distribution should be attained. However, it is recommended that the daily dose of K be given over a period of at least six hours.

The KCl is added from a concentrated solution to the fluids planned for a certain period of time —usually twelve to twenty-four hours. The solution which we use contains 2 mM KCl per ml, but the concentration is greatly reduced in the fluids injected. It is possible to give adequate amounts of K to infants at a concentration of 25 mEq or less per liter since the water requirement is high. In adults it is difficult to give the indicated amounts of K at a concentration less than 40 mEq per liter. Many physicians use higher concentrations, however very careful control is necessary if higher concentrations are used. Furthermore, concentrations greater than 40 are often painful when injected into veins.

The above rules make K therapy relatively safe if the disturbances in body composition and renal function are understood. Confusion will be avoided if the requirement of fluids for twenty-four hours is estimated. The deficit of water is likely to be 50 ml per Kg and is unlikely to be greater than 100 ml per Kg. The deficit of NaCl is likely to be equivalent to 20 to 40 ml of physiologic saline per Kg and only when Na concentrations are low will NaCl deficits be as great on the contents of 60 ml of physiologic saline. The water and NaCl may be given rapidly and thereby restore circularly and renal excretion. Although K deficits cannot be corrected rapidly, K should be started as soon as feasible, usually within two hours. The requirement for maintenance is added to the replacement of fluids. The former is computed on the basis of 125 to 150 ml per 100 calories of estimated heat production; about 3 mM of NaCl and 1 to 2 mM of KCl should be contained in each 125 to 150 ml of maintenance fluid. Except for about 20 ml of physiologic saline in 125 to 150 ml, the bulk of the maintenance fluid is five or ten per cent glucose in water. Additional KCl is added to provide 1 to 3 mM of KCl for replacement. The second day of therapy is the same except that only maintenance water and NaCl need be given, but KCl should be given at the rate of 1 to 3 mM per Kg per day. This form of therapy considers the magnitude of the deficits of water, Na, Cl and K, and the role of K in renal function. It has been safe and effective in our hands. The present studies show that K is necessary to prevent alkalosis when all fluids are given parenterally and food is not ingested. Addition of K is particularly necessary to prevent alkalosis after operation and is essential when gastric suction is used.

Pediatric Electrolyte Problems

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THE REALLY difficult assignment this morning, laying the groundwork for the presentation of what I hope will be some practical points in pediatric fluid therapy, has been ably handled by Doctor Darrow. I have chosen to talk largely about the management of pediatric surgical patients, for it is my opinion that other diseases requiring parenteral alimentation are of relatively less importance today than they used to be. It appears to me as a pediatrician in a children's hospital that the challenge of the postoperative management of the infant is a real one. Therefore, it is to the discussion of this problem that I would particularly like to call your attention.

First let us consider some basic assumptions.

1. It is obvious to all that when an individual stops eating he develops a deficit of sodium, chloride, potassium, probably of phosphorus, magnesium, nitrogen, and calories. In the absence of water intake, a patient will also become deficient in water. Therefore, logically, any parenteral fluid regimen must provide not only water and calories but also a variety of electrolytes.

2. It is probably easier to calculate the fluid requirements for an individual on the basis of surface area than it is upon the basis of body weight. It is my own feeling that it is also safer to use surface area in calculating fluid requirements since the major, possibly the only, safety valve provided in the body for the excretion of excess electrolytes or water is the kidney, and the capacity of the kidney to handle water and electrolyte is a function of surface area and not of body weight.

3. We assume that the body is better able to cope with parenterally supplied materials when these are given throughout a twenty-four-hour period rather than sporadically, for one, two or three hours several times during the twenty-four-hour period. Therefore, the regimen outlined will be a twenty-four hour regimen.

4. It is dangerous to administer potassium to a patient who has severe hemoconcentration secondary to dehydration. There are two reasons for this. One danger is that the serum potassium concentration may already be elevated; the second is that the kidney which normally excretes potassium is not functioning adequately because of a decrease in the glomerular filtration rate. Hence injection of potassium containing solutions under these circumstances may lead to toxic levels in the plasma.

5. There is a final, very important, assumption which is made and upon which the fluid program to be presented is predicated: any individual who has suffered trauma or stress, be it the stress of surgery, the stress of infection, or the stress of diarrheal disease, has lost potassium from his cells. The logical conclusion is, therefore, that any parenteral regimen designed to treat ill individuals should contain potassium. It is obvious that this does not apply to a patient with Addison's disease, it probably does not apply to a patient with chronic renal failure and it does not apply to certain other specific illnesses. But in the ordinary course of medical and pediatric practice, it seems to be a valid assumption.

Table I indicates the composition of the two main body fluid compartments; the extracellular and the intracellular. It also indicates the composition of two different fluids designed for parenteral administration. Both of these have 10 gm. of carbohydrate per 100 ml. of solution. Your attention is called to the fact that in extracellular fluid there is a difference between the concentration of sodium and chloride. This is a significant difference and probably should be maintained in fluids which are used for parenteral alimentation. We call the two fluids we use for parenteral alimentation polyionic solutions No. 1 and No. 2. Each is made up in 10 per cent dextrose and water and they are rather similar in composition to those

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originally described by Butler. You will notice that both of these solutions are quite dilute with respect to sodium, when compared to extracellular water. The sodium in extracellular water is about 155 mEq/L while these solutions have 30 and 57 mEq/L, respectively; in other words, one is one-fifth isotonic and the other is approximately one-third isotonic. You will also notice that there is more sodium than chloride in both of these solutions, and finally, that both of them contain potassium, some phosphate and that P.I.S. #2 contains magnesium.

Since there is a difference between the concentration of the sodium and chloride in these solutions, it is logical to assume that there must be some anion present to produce electrical neutrality. The anion present is lactate, but this does not mean that these are alkalinizing solutions. It simply means that lactate happens to be the convenient and biologically acceptable anion for the purpose. The pH of both solutions is about 7.4.

Table II indicates certain facts about the composition of milk. Since milk is the major source of food of most infants, I think it is important to examine its electrolyte content. Let us first look at mature human milk. You will notice that it is rather dilute with respect to sodium, rather concentrated with respect to chloride and that potassium concentration is greater than the sodium concentration. Cow's milk is used for the formula of most children and you can see that this milk is considerably more concentrated than human milk with respect to electrolyte. It is particularly generous in its sodium and chloride content. We conveniently dilute cow's milk with water in the usual infant formula but this nevertheless still provides a food considerably more concentrated

TABLE I.

COMPOSITION OF PARENTERAL FLUIDS AND BODY WATER

	meq/L				
	Na	Cl	K	PO_4	Mg
H_2O_E	155	110	5	3	2
H_2O_I	5	?	155	100	44
P.I.S. #1	30	22	15	3	-
P.I.S. #2	57	50	25	12.5	6

TABLE II.

COMPOSITION OF MILK

	meq/L		
	Na	Cl	K
Colostrum	18	32	22
Nature Human Milk	6	23	10
Cows Milk	30	42	35
Formula, 1/3 water	20	28	24
P.I.S. #1	30	22	15

with respect to sodium, chloride and potassium than mature human milk.

One of the important periods of life, when surgery is difficult but not infrequently necessary, is during the newborn period. Physicians then are faced with the problem of providing parenteral nutrition to newborn patients with illnesses such as tracheo-esophageal fistula, or other congenital intestinal abnormalities. I would like to remind you that a breast-fed infant of one, two, three or even five days of age is probably not going to get mature human milk but rather colostrum. Colostrum is considerably more concentrated in sodium, chloride and potassium than is mature human milk and is more like a cow's milk formula than human milk. Therefore, we feel, in this group of patients, it is sound to provide a solution for parenteral administration during the early neonatal period similar in composition to colostrum. Newborn infants with intestinal anomalies, although in need of surgery, are not deficient in electrolyte and water as is a child who has had diarrheal disease, or an infant who has had pyloric stenosis and has vomited for a week. These are patients who simply need maintenance amounts of fluid and we feel it is safe to administer a fluid whose composition is similar to the one we call P.I.S. #1. The amount administered should be similar to that which an infant would be receiving at breast or from a formula

TABLE III.

COMPOSITION OF INTESTINAL CONTENTS

	meq/L		
	Na	Cl	K
Nasogastric decompression (18)	46	72	7
Ileostomy, recent (adults)	130	115	11
Ileostomy, recent (child)	134	81	14
	116	90	12
	96	70	11
Ileostomy, adapted (adults)	45	20	3

TABLE IV.

FLUID REQUIREMENTS FOR A 1 M^2 INDIVIDUAL (30 kg.)

1% Glomerular Filtration Rate for urine:

100 L/M^2/24 hours: . . . . . 1000 cc

Insensible water Loss:

500 cc/M^2/24 hours: . . . . . 500 cc

Loss: 10% of body weight:

3000 cc

Try to replace 50% water:

Loss in 1st 24 hours: . . . . . 1500 cc

Total fluid required: . . . . . 3000 cc

In 2nd and 3rd 24 hour periods can replace remaining 50% of fluid loss: . . . . . 2200 cc/24 hours

that might be offered to a similar infant who is without disease.

Most patients who have gastrointestinal surgery also have a tube put into their stomach for the purpose of relieving distention. In the process of relieving distention, suction is applied and intestinal contents are removed. Table III records the average of eighteen determinations of electrolyte composition of material removed by stomach tube from six different children. You will note that there is more chloride than sodium in this fluid; this you might have expected, but the chloride concentration is considerably below that of plasma. I would like to call your attention also to the extraordinary amount of electrolyte which is lost in new ileostomies. You can see the dramatic change in salt content which occurs with adaptation and also the fact that the composition of ileostomy material of children and adults seems rather similar.

On Table IV is outlined the parenteral fluid program to which we subscribe at the present time. The data are indicated for a 1 M^2 individual; you may remember I mentioned that we were going to use surface area rather than weight as a basis for our calculations. We assume that an ideal urine volume is approximately one per cent of the glomerular filtrate which in a one square meter individual is roughly 1000 ml. per day. We assume that the insensible water loss is 500 ml/M^2/24 hours. It might be well to remember that a 30-kilogram individual is approximately one square meter. Any patient who is severely dehydrated has lost between 7 and 10 per cent of his body weight as water. In adults this figure can go considerably higher, but this is a useful one in pediatrics. Ten per cent of a 30-kilogram individual would be 3000 ml. We can only replace a limited amount of the initial loss in the first twenty-four hours, and a reasonable figure would be 50 per cent of that loss. That would mean that such a patient required 1000 ml. for urine,* 500 ml. for insensible water loss and 1500 ml. for replacement of his initial water deficit. Therefore, during the first twenty-four-hour period we would provide 3000 ml. of fluid for a dehydrated patient. Now the solution described on Table I, P.I.S. #2, was constructed so that if sufficient water be provided to a patient one would automatically provide sufficient electrolyte.

During the second and third twenty-four-hour periods, one tries to replace the rest of the 50 per cent deficit; this will be half of 1500 ml.; that actually makes a total of about 2200 ml. for the second and third twenty-four-hour periods. We have modified this to make it 2400 ml/M^2/24 hours only because it is an easy figure to remem-

TABLE V.

THEORETICAL FLUID AND ELECTROLYTE REQUIREMENTS OF 1 M^2 INDIVIDUAL REQUIRING ACUTE SURGERY

	ml	meq		
		Na	Cl	K
I.W.L	500	11	11	2
Continued Urine Loss	-	29	25	48
Usual Urine Loss	1000	17	13	13
50% Replacement	1500	112	82	27*
Ng. Suction	500	23	36	4
Total	3500	192	167	94
Amount Provided	3500	200	175	88

*The volume suggested for urine presupposes minimal renal work and a specific gravity of 1.012.

ber. Because the losses of water and electrolyte in urine may be quite high if disease continues beyond three days (the period after which we assume deficits have been met) we administer 2400 ml/M² utes. Such a solution given at this rapid rate initially expands the plasma volume and almost always results in urine formation. If, after the fluid is administered, a patient still has not voided (this

TABLE VI.

MAINTENANCE REQUIREMENTS OF FLUID AND ELECTROLYTE, 1 M² INDIVIDUAL

	ml	meq Na	meq Cl	meq K
I.W.L.	500	11	11	2
Continued Urine Loss	-	29	35	48
Usual Urine Loss	1000	17	13	13
25% Replacement	750	66	41	27
Ng. Suction	500	23	36	4
Total	2750	146	136	94
Amount Provided	2900	165	145	73

thereafter and as long as parenteral fluids are necessary. When some fluid is taken by mouth, this can be subtracted from the 2400 ml to be given by vein. Not included in Table IV is the program for a patient who requires parenteral alimentation but has no deficits of salt or water. This patient will require no more than maintenance amounts of fluid, about 1500 ml/M²/24 hours. If gastric suction is in use, the salt loss will be greater than otherwise hence P.I.S. #2 should be used not only for the basic fluid requirement, but also for replacement of losses from the gastro-intestinal tract. When there is no gastric intestinal suction, basic fluid needs can be met by P.I.S. #1.

To recapitulate, we provide 3000 ml. of fluid per square meter in the first twenty-four hours, 2400 ml per square meter thereafter. For the non-dehydrated patient, 1500 ml/M²/24 hours is sufficient. These are not absolute figures, but they are convenient to remember, and come close to the needs of most patients.

Because of the danger involved in giving potassium containing solutions to anuric patients, in dehydrated patients we use an initial fluid of one-third isotonic saline (50 mEq/L) in 10 per cent glucose as a hydrating solution. This is administered at the rate of 360 ml/M² in forty-five min-

is rare in our experience), the rate of fluid administration is reduced to 2400 ml/M²/24 hours and continued until the patient does void. After the hydrating solution has been given and the patient has voided, it is safe to start the potassium containing solution.

When there are losses by nasogastric suction, these must be measured and replaced ml for ml by an amount of P.I.S. in addition to the calculated twenty-four-hour requirement. In practice it has proven practical to add the extra fluid on the subsequent day, so that one can plan the fluid program for each day on the basis of the losses during the previous twenty-four hours. (P.I.S. # 2 Table VIII.)

Table V indicates the derivations of the electrolyte composition of P.I.S. #2. The volumes used in preparing this chart are similar to those used in Table IV; the electrolyte figures used have been derived from a number of different sources, but because of time limitations I shall not discuss them in detail at the present time. Since today we are particularly interested in surgical problems, I have included a theoretical fluid and salt loss by nasogastric tube. You can see that in supplying to this patient 3000 ml/M² plus the nasogastric loss, in theory, we have replaced

50 per cent of his previous water, and presumably, electrolyte loss and furthermore made available water, calories and salt for maintenance.* The asterisk after potassium in the "50 per cent replacement" column indicates that 24 mEq. represents only 25 per cent of the potassium loss, while the figures for water, sodium and chloride represent 50 per cent of the loss. There is a good reason for this: By use of K^{22} it has been demonstrated that only 25 per cent of a potassium deficiency can be replaced per twenty-four hours. Hence it seems unnecessary to provide more than 25 per cent of the deficit per twenty-four hours.**

TABLE VII.

PLASMA VALUES OF CHLORIDE AND BICARBONATE:

Effect of Potassium Therapy in Pyloric Stenosis

Day of Rx:	1	2	3	4	5	6	7	8	9	10	11	12	16
POTASSIUM													
CO_2 meq/L	38		38		32		31		-				25
Cl meq/L	100		-		70		84		94				103
NO POTASSIUM													
CO_2 meq/L						-		39	39	39			
Cl meq/L						75		71	94	80			

In Table VI similar data indicating that the requirement for fluids and salt on the second day is less than on the first. Instead of 1500 ml you need 750 ml for replacement. Otherwise, the figures are similar.

Now, let's look at something practical. Does this system work? You might ask, "Can you use one type of solution for treatment of patients with either acidosis or alkalosis?" Before answering this question, I would like you to recall something that I said initially: we can assume that all patients who are under stress unless given exogenous potassium will become deficient. Given time they will manifest symptoms of potassium deficiency and may even exhibit characteristic serum values, an increase in carbon dioxide and a decrease in chloride concentration, provided they do not die of other causes. In the normal course of events we do not wait for the exhibition of these changes, and furthermore, we know that the initial concentration of CO_2 in the plasma does not indicate the degree of potassium deficiency. Finally, we know that the serum K concentration neither necessarily reflects the concentration of this ion in the cells nor does it bear any predictable relation to the degree of overall K deficiency. Only in rather severe K deficiency does the serum level fall. In Tables VII and VIII are data from three patients, one with acidosis and two with alkalosis.

The first patient in Table VII had pyloric stenosis and was treated with sodium and chloride-containing solutions (as well as glucose) until the sixth day. You will note that he exhibited the conventional values for potassium deficiency; the bicarbonate was increased and the chloride decreased. Potassium administration was started on the sixth day; the chemical values of his blood improved and after operation on the twelfth day, the chloride and carbon dioxide were normal. Obviously this chart was not prepared to illustrate

*If one converts the total electrolyte loss to mEq. per liter of fluid lost, one obtains a solution about one-third as concentrated in respect to sodium as is extracellular water.

**This also means that at the end of three days, when the deficits of Na and Cl will have been completely relieved, only 50 per cent of the K deficit will have been made up. This is not a serious problem, however, for some of the K loss represents loss of protoplasm with its associated K, and so the cell need for replenishment of this ion is not as great as the total loss. Only when new protoplasm is made and deposited in the cell will more K be needed.

ideal management of pyloric stenosis. Rather we have chosen a patient who illustrates the failure of sodium chloride therapy and the success of potassium therapy in the presence of hypochloremic alkalosis. Tabulated on the same chart are data from a patient with pyloric stenosis who did not receive potassium, but rather normal saline. On the eighth day he received ammonium chloride intravenously in an attempt to correct the hypochloremia and you will see that on the next day his serum chloride was 94, but by the following day it was back to 80 mEq/L and the alkalosis was apparently unchanged. On the basis of what is known about blood pH in potassium deficiency, I think it would be safe to assume that both of these patients were initially alkalotic, even though we do not have pH values to prove it.

TABLE VIII.

D.D. 9 months — Day	1	2	3	4	5	6
Wt. kg. 8.02:	.	.	.	.	.	.
S.A. M^2 0.4:	.	.	.	.	.	.
Loss:	360	550	255	450	0	0
Intake: actual: cc	635	1200	1375	1350	1350	1495
Intake: theoretical:	.	.	.	.	.	.
Requirement cc	600	960	960	960	960	960
Loss cc	.	360	550	255	450	0
Total cc	600	1320	1510	1215	1410	960
Plasma Values:						
Cl meq/L	112	101	92	97	.	.
CO_2 meq/L	6	19	30	29	.	.
Total intake/ 24 hours cc:					1345	
Total theoretical intake/24 hours cc:					1275	

Table VIII contains data on both treatment and chemical values in the blood of a patient with an intussusception who was acidotic. I call your attention only to the figures for carbon dioxide and chloride. He entered the hospital with a CO_2 of 6 mEq/L and a chloride of 112 mEq/L and received the amounts and type of fluid predicted by our theoretical considerations. You will note that his acidosis was rapidly relieved (operation was performed on the first day), and he quickly returned to normal electrolyte equilibrium.

We have here what, from the chemical point of view, seems to be two entirely different situations. From the therapeutic point of view, however, it seems clear that both can be handled in the same way.

TABLE IX.

INADEQUATE POST-OPERATIVE MANAGEMENT

Pt: S.C. BCH #110 872

Age: 9 yrs.

Wt: 32 Kg.

S.A: 1 M^2

D_x: Congenital Dislocation of Hip

Parenteral fluids administered: 13 days

Total, L.			
Intake:			39.6
Output:	Urine	14.2	
	I.W.L. (est)	6.5	
	Ng. Tube	16.4	
			37.1

You might at this point raise an important question. Is it necessary to give parenteral fluids to all surgical patients? Probably not; however, we take the general position that almost all patients who have undergone abdominal surgery and re-

quire either the withholding of oral alimentation, or gastro-intestinal suction, need parenteral fluid therapy. A second question might also be posed at this time: Is the rule of thumb 2400 ml/M²/24 hours necessary or valid for all patients? Again the answer is "probably not." However, on the basis of theoretical data and clinical experience this seems to be a very safe amount of fluid and I prefer to supply fluid to an occasional patient who could get along without it than deny it to a patient who needs it.

TABLE X.

INADEQUATE POST-OPERATIVE MANAGEMENT

Pt. S.C. BCH #110 872									
Day		1 - 4	5	6	7	8	9	10	11	12
Theot. Deficit, ml		-9160	0	-1400	+100	-700	+100	-1400	-2100	-400
	Na meq		68	196	180	110	35	134	131	25
	Cl meq		40	170	70	88	22	118	110	23
	K meq		20	91	35	82	22	46	57	11
Plasma, meq/L										
	Na						133	138	138	142
	K					3.5	3.9	4.9		4.8
	Cl		96			75	75	78	84	87
	CO_2		21			42	40	45	36	37
	pH						7.59	7.45	7.45	

The data on Tables IX and X illustrate what happened to a child whose postoperative course was poorly managed. They illustrate what was a catastrophe, for a patient's life was lost because the assumption was made that only minimal amounts of parenteral fluid were necessary. This was a nine-year-old child who had a congenital dislocation of the hip, and came into the hospital for surgical correction of this defect. During a period of thirteen days, her intake of parenteral fluid was almost 40 liters. Her output was just a little bit less, so one might conclude from superficial examination that she got plenty of parenteral fluid. But three important errors were made in management. In the first place, she received only glucose and water for the first two days after surgery. Then, when she developed intestinal distention and hypochloremia, she received normal saline in large amounts. That would be a second error. A third error was made when her nasogastric tube was irrigated with tap water so that in essence she received tap water by mouth and the nasal gastric suction naturally withdrew fluid of the composition of gastric contents. She never did rally, and in spite of the fact that potassium administration was begun in modest amounts on the ninth day, she expired, apparently of severe electrolyte imbalance. The balance data in Table X are theoretical, since the figures were derived by subtracting actual intake from theoretical requirements in this case, 1500 ml/M²/24 hours plus loss by gastric suction.

Let me call your attention to the plasma values for sodium, potassium, chloride, CO_2 and pH. She received insignificant amounts of potassium until the ninth day, and on that day her pH was 7.59, her chloride was 75 mEq/L and her CO_2 was 40 mEq/L. Even during the period when she received potassium, unfortunately she continued to get tap water by mouth which was withdrawn by nasogastric suction. This patient's course illustrates the fact that it is possible for a child who has not had gastro-intestinal surgery to get into difficulties due to improper fluid management. It is probable that if this child had received proper parenteral fluids from the beginning, parenteral fluids containing potassium, she would have survived her surgery.

The next problem to concern us is that of the

management of patients with an ileostomy. In this situation there is one important rule to remember: you must treat the patient and forget preconceived ideas of fluid and electrolyte requirements. Fluid losses in an ileostomy may be enormous. Figure 1 indicates how much water can be lost by a patient with an ileostomy and how much replacement may be necessary. This was a child who weighed three kilograms and was followed for about forty days with an ileostomy. At times, during that period, it was necessary to provide as much as 70 per cent of his total body water by parenteral fluids and oral fluids simply to meet ileostomy losses. The chart indicates that in spite of these enormous amounts of fluid, he did not gain commensurate amounts of weight and hence, the fluid given simply replaced what was lost. Our experience with this patient led us to the conclusion that ileostomy losses should be treated the same as the losses by nasogastric suction. They should be replaced ml. for ml. by the solution being used for parenteral maintenance.

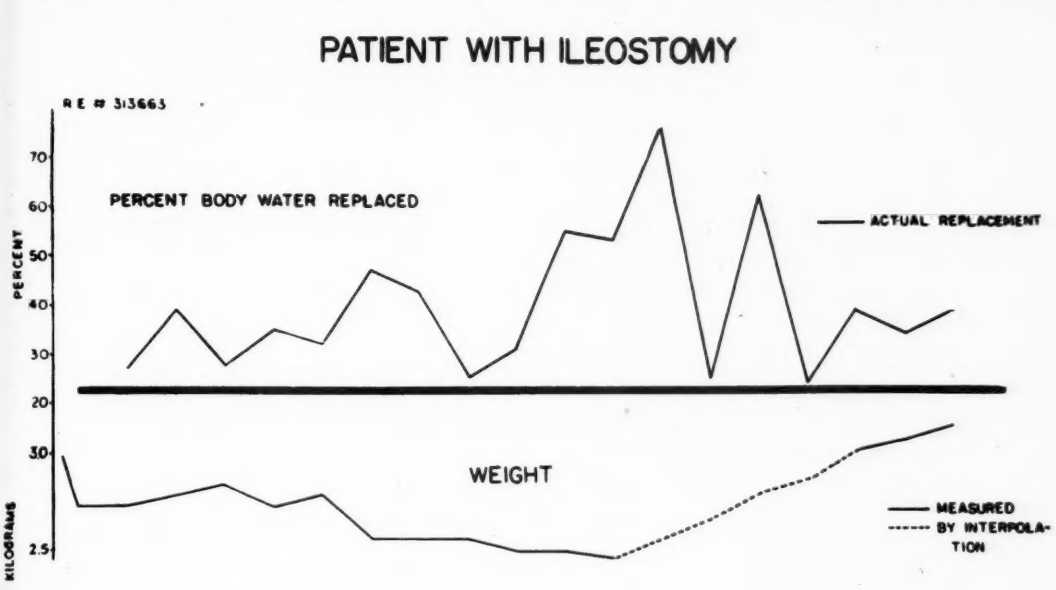

Fig. 1.

The child whose data are noted in Table XI had an ileostomy. He was a six-months-old infant weighing eight and one-half kilograms, who had a volvulus that required resection, and he required maintenance with an ileostomy for thirty days. During these thirty days, we followed the general plan outlined above using P.I.S. #2. Some of the details of therapy for the first eighteen days are indicated on Table XII. During this period we tried to make out a balance sheet based on theoretical considerations to compare actual intake and anticipated needs. Whether or not we were correct we will never know because we have no true balances, but we have the values of the plasma electrolytes and these usually reflect the efficacy of parenteral therapy. This child, who weighed eight and one-half kilograms, required as much as 2,000 ml a day by vein, which was as much as 50 per cent of his total body water; but,

TABLE XI.

MANAGEMENT OF ILEOSTOMY, INFANT

Pt:	D.H. BCH #176 364
Age:	6 mo.
Wt:	8.5 Kg.
S.A:	0.4 M^2
D_x:	Volvulus with resection

Parenteral fluids administered: 30 days

except for a period between the sixth and ninth day (the resection was done on the second day), the electrolyte values in the serum remained near normal. We collected the ileostomy output just as we would have collected nasogastric tube contents, measured the volume and replaced it ml for ml with the type of fluids outlined. This child was managed entirely with P.I.S. # 2.

We felt that we could have given less fluid to this patient if we had used a more concentrated solution. Therefore, in subsequent patients we have used a solution more concentrated with respect to electrolyte. Its composition is indicated on Table XIII.

The data which follow demonstrate what can be done in comparing anticipated requirements based on the assumptions mentioned above with actual needs as measured by balance data. Table XIV indicated the clinical data of a child with acute ulcerative colitis who had a resection of

TABLE XII.

MANAGEMENT OF ILEOSTOMY, INFANT

Pt: D.H. BCH #176 364

18 days

Theot. water req., L	20.3
Act. water intake, L	22.6
Theot. Balance, ml/day	+130

Day	1	2	3	6	9	11	18	27
Weight, Kg	7.0			8.7	8.9	8.1	8.0	7.4
Plasma, meq/L								
Na		139	135	132	125	131		
Cl	107	100	99	80	82		100	103
K		3.7	3.0	3.2	3.3	5.1		
CO_2	22	19.7	27	34	35		30	27.5

TABLE XIII.

SPECIAL SOLUTIONS FOR PATIENTS WITH ILEOSTOMIES

meq/L	
Na	100
Cl	75
K	30

TABLE XIV

MANAGEMENT OF ILEOSTOMY

Pt: J.G. BCH #199 321

Age: 8 yrs.

Wt: 20 Kg.

S.A: 0.75 M^2

D_x: Acute Ulcerative Colitis

Parenteral Fluids Administered: 14 days

Total, L. (12 days)

Intake:			37.9
Output:	Urine	15.4	
	I.W.L. (est.)	4.2	
	Ng. Tube	0.65	
	Ileost.	15.7	
			35.95

her colon and an ileostomy and required parenteral fluids for fourteen days. During this period her intake was 40 liters and her output was 35 liters. Her ileostomy loss during that period was about her course. I would like to call your attention to the fact that her CO_2 remained almost normal throughout the total period of parenteral fluid administration. Her chloride fell at one point but

TABLE XV.

MANAGEMENT OF ILEOSTOMY

Pt: J.G. BCH #199 321								
Day		1	2	3	4	5-9	10	11	12
Theoret. Water Balance		-300	+269	+270	+510	+ 10	+ 25	+1395	- 85
Body Wt., Kg.		19.7	18.5	20	20	19.5	19	19	
Plasma, meq/L									
	Na		135	140	142	143	133	140	137
	Cl		93	93	95	92	87	94	97
	K		4.1	6.2	5.7	5.7			
	CO_2		29.6	33	26.5	27	24.5	26	26
	pH			7.29	7.44	7.25	7.32	7.30	7.42

TABLE XVI.

MANAGEMENT OF ILEOSTOMY

Pt: J.G. BCH #199 321

Intake, Day		1 - 7		1 - 12	
		Act.	Theot.	Act.	Theot.
H_2O	L	21	18.8	37.9	35.86
Na	meq	2098	1915	2978	3587
Cl	meq	1577	1436	2349	2684
K	meq	630	574	1172	1075

Theot. Daily Balance			
H_2O	ml	+300	+170
Na	meq	+ 26	- 51
Cl	meq	+ 20	- 28
K	meq	+ 8	+ 8

a liter per day. You can see that her replacement needs were very large. We used the solution indicated in Table XIII exclusively.

Table XV records some of the data concerning then rose toward normal and on the twelfth day was almost normal.

Table XVI is an attempt to make a balance of her data. The intake and balance per day

are recorded in two grouped periods; days one through seven and one through twelve. The theoretical data represent what we think she should have had, and the actual data represent what we succeeded in providing. This discrepancy is the result of technical difficulties such as needles coming out of veins, etc. The division into two periods was necessary because the patient started to eat after the seventh day, and her food was largely milk. Unfortunately, milk is a poor source of electrolyte at least when it is used to replace salt lost from an ileostomy (see Tables II and III) and the negative theoretical balance is the result of this. The theoretical balance represents the difference between what we think this patient needed and what she actually received. During the first seven days, she should have been in a positive balance with respect to water and electrolyte. As soon as milk was substituted for a portion of the parenteral intake she went into a theoretically negative balance of sodium and chloride, but, since milk is fairly high in potassium she probably did well with respect to that ion.

TABLE XVII.

MANAGEMENT OF ILEOSTOMY
BALANCE DATA

Pt: J.G. BCH #199 321

Cumulative Balance, Days 2, 3, 4	Retention/24 hrs Theot.	Actual
H_2O, ml	+349	+281
Na, meq	+ 33	+ 10
Cl, meq	+ 26	+ 30
K, meq	+ 10	+ 7

Fortunately, we were able to collect and analyze excreta and obtain accurate balance data on days 2, 3, and 4. Table XVII* is a tabulation of this information. We avoided trying to measure losses on the day of surgery because we would have had no way of estimating the electrolyte which was lost when the colon was lifted out of the body; therefore, we started our balance studies on the second day and have charted them as cumulative data. Theoretical retentions taken from Table XVI are compared with the measured retentions. You will see that there is a rather surprising agreement between these two sets of data. In other words, on the basis of theoretical thinking, we were able to calculate the right amount of salt and water for this patient. We have data like this on other patients which lead us to believe that it is possible on the basis of theoretical assumptions to come quite close to approximating the needs of children during the postoperative period and after ileostomies.

*Taken from unpublished data: Lowe, C. U. and Calcagno, P. L.

Conclusion

In closing, I would like to recapitulate the rules of thumb which we use for managing postoperative infants. I think the most important one is to treat a patient, not chemical values of plasma. Measure intake precisely and output if possible. Irrigate nasogastric suction not with tap water but with either a polyionic solution or, if necessary, with a half normal saline solution. Remove nasogastric suction tubes as soon as possible. Patients do better without a nasogastric tube in place. The blood or plasma administered should not be included as a component in calculations of water intake. Replace nasogastric or ileostomy losses ml for ml with whatever solution has been deemed necessary for that patient. Weigh a patient initially and daily. Weights are very simple things to get and are helpful in trying to check the efficacy of a fluid regimen. Use dilute solutions; do not use normal saline. We think half normal saline is probably too concentrated for many patients; third normal saline is better. Try to use a solution in which the ratio of sodium to chloride is similar to that which exists in the plasma. In general it is possible to use the same solutions and volumes for acidotic and alkalotic patients. For maintenance requirements of newborn infants without unusual losses, use a solution similar in composition to colostrum, like P.I.S. #1; for older children use P.I.S. #2, and for patients with an ileostomy make up a solution similar to that on Table XIII. For following a patient's electrolyte balance it is probable that it is sufficient to determine the CO_2 and chloride content of plasma.

Give 3,000 ml/M^2 for a dehydrated patient dur-

(Continued on Page 32)

Development and Correction of Electrolyte Disturbances Associated with Salt Retention

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FROM the standpoint of salt and water metabolism, the body may be regarded as a series of differentiated fluid phases separated by discriminating cell membranes. For clinical purposes, it is convenient to divide these fluid phases into an intracellular phase and an extracellular phase.

The extracellular phase, in turn, consists of the blood volume and the interstitial fluid volume. Edema represents an expansion of one component of the extracellular phase, the interstitial fluid. It always develops under circumstances where, for one reason or another, the kidneys retain excessive amounts of salt and water that have either been ingested by mouth or administered parenterally. Under these circumstances both salt and water accumulate in the body, selectively become deposited in the interstitial fluid, and should the magnitude of this accumulation be sufficient, pitting edema becomes evident. Salt retention under most circumstances appears to be the primary initiating event secondary to which water is retained. The consequences of salt retention, therefore, become very important to evaluate under circumstances where edematous states exist. We know from clinical evaluation of a variety of different disease states that many different disorders are characterized by edema (i.e., cirrhosis of the liver, nephrosis, and congestive heart failure are all, in part at least, associated with massive accumulations of salt and water).

The significance of this salt and water accumulation, however, is not as readily apparent as it would seem at first sight. Everybody agrees that these large accumulations are mechanically deleterious in the sense that they are unsightly. They deposit in the legs leading to ulcers. They may deposit in the gastro-intestinal regions leading to impaired appetite and gastro-intestinal symptoms of one kind or another. It is important to evaluate in addition to these mechanical effects of salt and water retention those effects which may have more profound physiological significance. This is particularly true in the case of congestive heart failure.

In order, therefore, to approach the importance of salt and water retention as well as the measures which may be applied to rid the body of this excessive accumulation of fluid, it is well to evaluate on the basis of current information at least what might be the sequence of events leading to the retention of salt and water.

Initially, in some sense, the heart fails. Precisely what this means today cannot be defined, but it appears at least to be accurately described by the following:

It is clear from Starling's law that the force of systolic contraction is directly proportional to the amount of disastolic stretch up to a point beyond which the force of systole declines with increased disastolic stretching. It is thought by many, therefore, that during the course of heart disease, arteriosclerotic heart disease, or hypertensive heart disease, the myocardial fiber is injured and can no longer expel the blood that is returning to it with the same force as in the normal state. Under these circumstances, a tiny increment of blood remains within the heart, causing diastolic stretching and thereby facilitating a more forceful systole. As heart disease progresses over a period of years, the amount of blood within the cardiac chamber mounts at times to astronomical proportions.

Bing has estimated, for example, that in chronic congestive heart failure there may be as much as 800 or 1000 cc. remaining within the cardiac chamber and in diastole. This large accumulation of blood during diastole permits stretching of the myocardial fiber and thereby permits the heart to expel a normal or near-normal cardiac output. But the price the individual pays for maintaining the cardiac output at near-normal level is a marked rise in the diastolic filling pressure. After a period of years, this pressure rises to a point where the central venous pressure increases. The cardiac output under such circumstances may be nor-

mal, may be higher or may be lower. Whatever it is, the key point is the fact that there is a resistance, a high pressure within the ventricular chambers, as a consequence of which the flow of blood toward the heart is impeded and backed up.

The consequences of this increased pressure are clear again from the Starling equilibrium. When venous pressure rises there is a tendency for transudation. This in turn causes a shrinkage of blood volume so that there is a redistribution of extracellular fluid. The blood volume decreases, interstitial volume expands, but the total extracellular volume remains unchanged. At this point, however, as a consequence of something which is not clear, this disequilibrium causes the kidneys to react by retaining salt.

This reaction has been ascribed by some to a decrease in blood volume. Others have implicated a low cardiac output. Still others have considered increased venous pressure as the stimulus to cause the kidneys to retain salt. Whatever it is, the kidneys respond to the congestive state by a tenacious retention of salt and water so that virtually no salt may appear in the urine. And this retention is largely a consequence of enhanced tubular reabsorption of sodium. This enhanced tubular reabsorption of sodium, in turn, leads to a concomitant retention of water, and therefore edema forms. At this point, a series of reactions ensue which are a direct consequence of edema formation. Precisely what the steps are in this reaction are not clear but it has been suggested that in some manner the formation of edema reexpands the blood volume to normal or perhaps supernormal values; this, in turn, increases the central venous pressure, thereby augmenting the magnitude of the congested state so that a vicious cycle appears to be set up by the failure of the heart where edema formation in a certain sense aggravates heart failure.

In the work of the British investigators, Pugh and Windom, an attempt was made to study precisely what effects ridding the body of salt and water alone might have in a patient with severe congestive heart failure. They found that when patients in severe heart failure were given mercurial diuretics, there was a marked fall in right auricular pressure. At the same time, the cardiac output rose and both of these, in turn, were correlated with a rising urine volume.

It appears, therefore, from studies such as these that ridding the body of salt alone by an agent whose sole action, according to present views, is on the kidney, has no direct effect on the heart whatsoever; ridding the body of salt may cause a precipitous fall in right auricular pressure and thereby improve the cardiac output and lead to some relief of the congested state. At present, it appears that in congestive heart failure ridding the body of salt accomplishes more than merely relieving the mechanical effects of fluid accumulation. There is a direct physiological effect. The mechanism may be unclear, but in some manner cardiac function is improved.

In order to approach this problem, it is well to turn to a consideration of those measures which are designed to correct the congestive state as it exists.

Pre-eminent in the treatment of heart failure is the use of digitalis with bed rest. This is true for several reasons. First, digitalis acts only under circumstances where congestive heart failure exists. It is not a diuretic under any other circumstances. Edematous states where heart failure is not present do not respond to the action of this agent. So under these circumstances, a successful digitalis diuresis is strong evidence for the existence of heart failure where a problem of differential diagnosis exists.

Second, a digitalis diuresis is always a physiological one in the sense that digitalis never causes a distorted loss of salt and water. It never disrupts the electrolyte composition of plasma; it never causes excessive loss of fluid. Digitalis, therefore, is a safe diuretic procedure in the sense that it reverses partially or completely the sequence of events which initially led to congestive heart failure.

Supplementing the use of digitalis with rest is a very important measure, because rest facilitates a fall in the work of the heart, for under more nearly basal conditions the individual does not have those demands for a high cardiac output which work imposes. If, therefore, one were to assign some sequence of events in the treatment of patients with congestive heart failure, one would assign pre-eminent importance to digitalis and to bed rest. Bed rest does not mean necessarily in bed; a cardiac chair or some similarly comfortable mode of resting is perfectly adequate.

In many instances, patients with severe congestive heart failure, adequately digitalized and provided with adequate rest, nevertheless fail

to deliver their edema. Under these circumstances, one turns to other measures which may promote the renal excretion of both salt and water. Of these measures, mercurial diuretics are perhaps the most important as well as the most potent.

The urine of a prone, dehydrated man shows a marked excretion of sodium about an hour and a half to two hours after 2 cc. of mercurial diuretic has been injected. The excretion of sodium excedes the excretion of water. In other words, mercury is causing here a selective excretion of sodium in excess of water. And as might be predicted, under such circumstances, the concentration of sodium in the serum falls slightly. Later, there is a moderate acceleration of potassium excretion and the excretion of acid (ammonium simultaneously with titratable acidity rises). So, if we turn to the normal individual, then there are several effects which deserve comment.

There is first, as a consequence of mercurial action, an accelerated excretion of salt in water, but salt in excess of water. There is a moderate loss of potassium; there is increased acid excretion into the urine.

Urine output decreases as the excretion of solutes rises more or less in a linear fashion. Apparently mercury causes an accelerated excretion of water as a passive consequence of the excretion of salt. The loss of water appears largely, but not entirely, to be secondary to the accelerated excretion of sodium. A tiny increment of water excretion is due to the fact that because sodium is lost in excess of water, there is a transient inhibition of the posterior pituitary function resulting in a slight water diuresis during the later period. But by all odds, the major cause of the accelerated urine flow is accelerated solute excretion, and this, in turn, consists largely of the accelerated excretion of sodium.

In Wallace's data, the effects of mercury in a patient with congestive heart failure are noted. Here a very salutory diuresis has occurred which is normal in every respect. Sodium is lost with chloride in the same proportions in which they exist in extracellular fluid. There is no negative balance; potassium loss more or less parallels sodium loss. Serum concentrations are normal. Another situation exists, according to Wallace. Again mercury is given under repeated instances and here there is a loss of chloride far in excess of sodium. Accompanying this loss, there is a marked negative balance of potassium and here, in a way similar to Dr. Darrow's studies, there has supervened a marked alkalosis. The serum bicarbonate approaches almost 45 mEq. per liter and the serum chloride falls to almost 70 mEq. per liter. In other words, a mercurial diuresis has been accompanied by potassium deficiency and metabolic alkalosis, and the patient becomes refractory to mercury. This, then, is one of the causes of the refractory state. The cause of this potassium loss and the cause of the alkalosis are not clear, but I should like to mention one possible mechanism whereby this might be effected.

This is illustrated by the effect of the administration of ACTH and salt to a normal man. Under the circumstance where a patient is on a constant diet, there is a marked loss of potassium in excess of nitrogen accumulating to some 200 mEq. after ten days. At the same time, sodium and chloride are retained in the body, but sodium markedly in excess of chloride. This retention of sodium in excess of chloride can be shown, as Dr. Darrow has shown in his rats, to be a consequence apart from the fact that some of this retained sodium is not retained with chloride in the extracellular fluids but penetrates into tissue cells in exchange for potassium. While these changes are going on in the urine, one can detect a fall in the concentration of serum potassium and a fall in the concentration of serum chloride, despite the fact that the balance of chloride is negative.

The most noteworthy observation to which I would call your attention is the supervention of a metabolic alkalosis. The urine concomitantly exhibits a marked acceleration of acid excretion. Actually, after a period of ten days, the loss of acid approaches some 400 mEq. Therefore, it is necessary to suggest some hypothesis which might explain this marked alkalosis and potassium deficiency. Sodium reaches the distal tubule where under the impact of ACTH, cortisone or, as I shall try to argue, under circumstances of mercurial diuresis, it exchanges for potassium, and potassium is lost into the urine. This, in turn, leads to potassium deficiency. When potassium deficiency develops in this way, cells appear to yield their potassium with increasing restraint and, as a consequence, sodium begins to exchange with

other cations, the principal one being acid cation.

If we examine what might proceed in the tubular cells, we can imagine the hydration of CO_2 and water under the impact of carbonic anhydrase leading to H_2CO_3. Sodium, in turn, may exchange with hydrogen causing an increased excretion of titratable acid. But the principal way sodium causes acid loss is by an exchange with ammonium. This is, by no means, the only mechanism whereby acid may be lost; there is doubtless a large loss of acid into the tissue cell. But here I would emphasize the fact that under circumstances where potassium deficiency develops, there is a marked loss of acid into the urine and that this loss of acid into the urine contributes in part at least to the development of alkalosis. From the standpoint of mercurial diuresis, this is exceedingly important because in cases where potassium deficiency develops, where alkalosis supervenes, individuals become refractory to the action of mercury. In addition, one has to cope with the deleterious consequences of potassium deficiency itself.

There are a number of symptoms which arise in association with potassium deficiency. First, there are the fairly specific symptoms. These are quite unimportant in most instances by virtue of the fact that they are so rare in their occurrence. If one has to rely on flaccid paralysis, one would practically never diagnose potassium deficiencies.

Second, there are a group of exceedingly important but highly non-specific symptoms which supervene. I say highly non-specific because any sick patient may exhibit these difficulties in varying degree. Perhaps the most important feature, from a clinical standpoint, which should lead to a suspicion of potassium deficiency is a clinical appraisal of those circumstances likely to produce potassium loss. Mercurial diuresis is surely outstanding in this respect in the cardiac patient, but it should be noted that some cardiac patients vomit, or become anorexic and do not eat. Recurrent injections of mercury, starvation and vomiting all are apt to produce varying degrees of potassium deficiency. Electrocardiographic evidence is of a non-specific type, but is helpful. There is prolongation of the QT interval, T wave inversion and ST segment depression, and the presence of a prominent U wave. These evidences of a potassium deficiency are not specific. Many diseases of the myocardium may eventuate in such disturbances, but if they are quickly reversed by potassium administration hypopotasemia is a likely cause.

Chemical evidence, such as a low concentration of serum potassium hypochloremia and alkalosis, is important. It should be pointed out, however, that hypochloremia is not an invariable accompaniment of serious potassium deficiency. Alkalosis, especially when it persists after salt and water replacement, is suggestive of potassium deficiency. This stipulation applies less to the cardiac patient; inasmuch as he is already edematous there is no shrinkage of extracellular volume, rather an overexpansion. But the supervention of alkalosis is one of the most suggestive features pointing to the existence of an underlying potassium deficiency.

Such considerations can probably be applied to the sequence of events in mercurial diuresis. Mercury may act by inhibiting the proximal tubular reabsorption of sodium, and as a consequence excessive amounts of sodium and water are delivered to the distal tubules. In normal subjects and in patients who are responsive to the action of mercury, the capacity of the distal tubule to reabsorb sodium is exceeded, and under those circumstances sodium excretion is accelerated. The accelerated excretion of sodium in turn obligates water leading to an accelerated urine flow. In addition, the slight hyponatremia, which is caused by a loss of sodium in excess of water by this process, may cause some inhibition of posterior pituitary secretion, as a consequence of which a mild water diuresis supervenes.

In patients who are refractory, it can be hypothesized that mercury, which is a tubular poison, may inhibit the sodium reabsorption just as it does in normal subjects but that the capacity of the distal tubule to reabsorb sodium is enormous. The stimulus for sodium retention is very intense, and as a consequence sodium is reabsorbed and part of this sodium is reabsorbed in exchange for potassium. Under such circumstances, potassium deficiency develops and potassium deficiency developing here may have the same consequences as potassium deficiency developing under the impact of sodium and DOCA which Dr. Darrow has earlier described. There is a change in muscle composition, hypochloremia of the serum may occur, and there tends to be a real loss of acid as ammonium titratable acidity in hydrogen leading in part to an alkalosis.

So, if we regard the effects of mercury, there

are certain effects which this substance has that are serious and deleterious.

First, there is shrinkage of extracellular volume. It is usual for a mercurial diuresis to proceed to a point where the edema is delivered and then often the patient becomes refractory to the action of mercury. In a sense, this is a protective feature. Occasionally, as in the normal subjects who are practically thrown into salt depletion shock by 2 cc. of mercury, this diuretic agent can shrink extracellular volume below normal levels. Under those circumstances, serious renal impairment may supervene; not due to any poisoning of the tubular cell necessarily, but a consequence of a shrinkage of the extracellular fluid. The safest way to circumvent this complication is simply to stop giving mercury under circumstances where peripheral edema has been delivered, even though perhaps some rales may be in the chest.

Second, there is the low salt syndrome which has not been considered here in detail. This is a consequence of the fact that there is a loss of salt in excess of water, in a net sense, that water is retained, and this sometimes supervenes after a massive mercurial diuresis. Under such circumstances, it is correctable by the administration of hypertonic saline although admittedly patients who tend to develop this disturbance often will develop it even under circumstances where mercury is withdrawn and salt is administered. They tend to retain water despite anything one can do.

Third, potassium deficiency is apt to supervene, and it is important to recognize that one cause of failure to respond to the action of mercury as a diuretic is the supervention of a deficit of potassium.

Finally, a hypochloremic alkalosis may supervene, and this complication is in part perhaps a consequence of the loss of acid into cells and part a consequence, as I have tried to show, of the excretion of acid into the urine. These features of mercurial action are responsible in part, I think, for the so-called refractory state of mercury. And in any patient who fails to develop a mercurial diuresis, it is important to stop the administration of mercury and to evaluate the possible causes which may have led to his refractory condition. These causes, such as are known, have been partially listed here. The diagnosis (and detection) depends again on a high index of suspicion when refractoriness exists. If one thinks of potassium deficiency; if one thinks of alkalosis; then these disturbances can often be readily detected.

Some physicians have been accustomed to administer mercurial diuretics with one or two grams of potassium chloride for a day or two preceding and accompanying the injection of mercury. In other instances, this may not be necessary, of course, if the patient is eating well. In any event, the supervention of a refractory state should lead to a suspicion that this exists.

Should potassium deficiency exist, it is important to correct this. Four grams or so of potassium chloride can be given by mouth, diluted in some suitable vehicle, to supplement the oral intake of potassium in the diet. In addition, it is extremely important to administer ammonium chloride for reasons which are not clearly understood. Some cardiac patients do not correct their alkalosis with potassium alone, and under such circumstances the administration of an acid load may restore the refractory state. Three or four grams of ammonium chloride administered before and during the injection of mercury, that is, under two days preceding and under two days following the injection of mercury, may restore a refractory patient to a responsive state.

It should be emphasized that the mercurial refractory state is in part reversible. For this reason, it is important to evaluate the causes which lead to refractoriness. Prominent among these causes are potassium deficiency, metabolic alkalosis, salt depletion and hyponatremia. By a high index of suspicion, one can often detect the responsible agency and institute measures to correct this effect.

Vehicles and Volume, with Special Reference to Amino Acids and Sugar

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THE SUBJECT of parenteral feeding is a very important one, and the attendance at this meeting attests to the interest that you all have. I suppose, too, in a way it indicates the fact that there is still much we have to learn about the subject.

The United States is known in the rest of the world for many advances in medicine and in surgery, and one of the things that the visitors from overseas like to know about is our use of parenteral fluids. But some, when they come over, get a little confused. One of them, a surgeon from Calcutta, India, wrote me from New York City as follows:

"I came here to find out about parenteral fluids and I visited a professor in one of the big medical schools, asking him how he gives parenteral fluids. He referred me to the resident surgeon and I met the resident surgeon and I asked him the same question, and he referred me to the assistant resident surgeon. And the assistant resident surgeon said, "Well, the intern takes care of those matters," and he referred me to the intern. The intern was very busy and he said he'd like to have me talk to the fourth-year medical student and I talked to several of them and found that their answers were all different."

Now in discussing the subject of parenteral feeding, I first of all would like to pay a tribute to Dr. Carl Rice who, without really direct University support and, initially at least, at his own expense, has been able to add so much to our knowledge of a more complete type of parenteral feeding. He has done this in at least three ways, all based upon careful bedside clinical observation as well as meticulous scientific measurements. For instance, he has added much to the technique of administering parenteral fluids with the least discomfort and danger to the patient. Second, he has shown that the addition of alcohol is not only feasible and practical, but achieves much higher caloric intake than is possible without its use. Third, as an able physician and surgeon, he has demonstrated the beneficial bedside influence which followed the maintenance of a good nutritional intake despite the fact that the patient cannot take anything by mouth. The last objective, of course, is very obvious to anyone who believes firmly that starvation is not only not harmless but is actually harmful, but yet this simple statement needs continuous emphasis.

I would like to emphasize, too, that parenteral feeding never has and never will compete with oral feeding. It competes only with starvation as a temporary method really designed to enable the patient to eat sooner. While too much parenteral fluid tends to be used, the remedy is to use these fluids only when indicated in as small amounts as necessary but to make a mixture as complete as is feasible.

Now in participating in this symposium it was suggested that I discuss some of the newer observations which we have made, particularly with the use of invert sugar and fructose. I am afraid I won't be able to say much about invert sugar because we have made few observations. However, since it contains 50 per cent fructose and glucose, my own feeling is that it somehow has effects half way between those of glucose and fructose.

However, I would like to expand my discussion in order to bring to you some of the fundamental studies made by others as well as by ourselves on the important question of how many calories are needed in order to utilize amino acids. I say this particularly because statements have been made in the literature that there is no use infusing amino acids unless you give the patient full caloric intake. Now this argument may seem academic, but it has resulted, I am afraid, in a widespread belief that until intravenous fat is available to fill out the normal caloric intake, there is no use in adding amino acids to the usual glucose which still forms the basis for most

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programs of intravenous feeding. These statements, however, have completely ignored and overlooked the work of Dr. Rice and his co-workers, as well as observations by many others, showing that nitrogen balance can be achieved with less than a full caloric intake and that even if it is not achieved, the degree of negative nitrogen balance is considerably reduced when amino acids are added despite a suboptimal caloric intake. I would like to express this by saying that if you can't give a whole loaf as Dr. Rice does, at least a half a loaf is better than no loaf.

NUTRITIONAL COMPOSITION OF THE HUMAN ADULT MALE*

Total Weight	70.6 kg.
1. Water	48 kg.
2. Protein	10 kg.
3. Fat	9 kg.
4. Ash	3 kg.
5. Carbohydrate**	0.6 kg.
6. Plus Vitamins	

* Approximate values from Mitchell et al. J.B.C. 158:625, 1945
** From Everett, Medical Biochemistry (Hoeber) p. 306

Fig. 1. Nutritional composition of the human adult male. (From Elman, R.: Surgical Care. New York: Appleton-Century, Crofts, 1951)

Now first I would like to show in Figure 1 the nutritional composition of the human adult. Any time a patient does not receive an adequate amount of food of any kind he subsists only by using his own tissues. When you look at this table you can see that there is really only one dispensable food material and that is adipose tissue. There is actually very little carbohydrate in the body and although there is considerable protein, it is generally agreed that the use of protein for energy leads to functional impairment.

For example, liver and plasma protein, and hemoglobin are used from the very beginning of the time that the diet is deprived of protein. The problem of water I might pass over very simply. It has been discussed many times today and it is a simple one because under normal conditions 2 liters is adequate in the average-sized adult under standard conditions. I will not discuss it further except to say that as I see parenteral fluids used in various parts of the country, too much water is usually given. This has been well-emphasized in the comments of Dr. Ariel. Our objective in preparing any diet is to prevent or correct important deficiencies in the body and the one I am going to consider this afternoon is protein.

There are three degrees in this objective: first, to spare protein, *i.e.*, to maintain nitrogen balance; second, to build protein if there is a deficiency, *i.e.*, to achieve positive balance, and, third, to lose as little protein as possible by reducing the degree of negative nitrogen balance. All of these objectives are easy if you are able to give a full intake of say 4,000 calories and 200 grams of protein, but such an intake is impossible in at least two conditions about which I know. One is the severely malnourished patient unable to take so much food by mouth (at least in the beginning), because of severe gastrointestinal disturbances, and the other, during parenteral feeding. Now nitrogen balance within certain limits is a fairly good measure of protein loss or utilization, but other methods have also been used. In the following discussion I would like to point out that while an adequate caloric intake maintains the best type of positive nitrogen balance, there are many other factors which are also important in promoting the synthesis of protein tissue as measured by this or other means. One of them is the state of nutrition of the patient.

NITROGEN BALANCE IN 13 MALNOURISHED PATIENTS ALIMENTED PARENTERALLY ON A SUBCALORIC DIET

2 liters daily of 5% amigen + 5% glucose
total caloric intake = 800 calories

	Body Weight in % of Normal	Daily Nitrogen Intake (Gms.)	Daily Nitrogen Output (Gms.)	Daily Nitrogen Balance (Gms.)
Average	65.4	12.6	7.1	+5.5
Range	55-78	12.6	4.5-11.1	+1.5-+8.1
Standard Deviation	6.8	0	2.1	2.0

Fig. 2. Nitrogen balance during malnutrition on a low caloric intake. (From *Surgery*, 34:874, 1953)

The first data are from J. B. Allison (Fed. Proc., 10:676, 1951). They represent nitrogen balance on an inadequate caloric intake containing protein. Dogs which are malnourished at the start go into positive nitrogen balance immediately whereas well-nourished dogs go into negative balance. They both tend to approach zero as time goes on. Nitrogen balance on a protein free intake in either case would, of course, result in a marked negative balance.

We have confirmed this phenomenon as shown in Figure 2 of our own data in a series of patients. Thirteen malnourished patients were on the subcaloric intake containing 12.6 grams of nitrogen

as hydrolyzed protein. Note that all of these patients were in positive nitrogen balance to the extent of +5.5 with a range of 1.8 to 8.1.

To show the influence of malnutrition, we repeated the same experiment on three patients after they had become repleted. You can see (Fig. 3) that the positive nitrogen balance either became less or became negative. That doesn't mean that the amino acids were not being utilized, because if they had had glucose alone, they would have been in a —6 to —8 grams of negative nitrogen balance. The point is that the more malnourished the patient is, the more able he is to utilize amino acids despite the fact that we cannot give him a complete caloric intake.

COMPARATIVE NITROGEN BALANCE IN 3 MALNOURISHED PATIENTS ALIMENTED PARENTERALLY ON A SUBCALORIC DIET BEFORE AND AFTER PARTIAL REPLETION

Case	Body Weight in % of Normal	Average Daily Nitrogen Balance	
		Before Partial Repletion	After Partial Repletion
G. S.	75	+2.1	-3.3
N. Y.	64	+1.5	-2.3
N. B.	78	+7.7	+1.7

2 liters daily of 5% amigen + 5% glucose
total caloric intake = 800 calories

Fig. 3. The effect of repletion on nitrogen balance on a low caloric intake. (From *Surgery*, 34:874, 1953)

Figure 4 deals with a time factor on which I will spend just a few moments. It shows that if you give calories and protein, they must be given simultaneously. That is true whether you give them by mouth or parenterally. This was an experiment on a very malnourished patient with terminal cancer. We gave him one liter of 10 per cent glucose morning and afternoon; the negative nitrogen balance was marked. In the middle period we gave 5 per cent glucose in amino acids mixed together morning and afternoon and now nitrogen balance was positive. When we gave the same amount of material divided into 2 liters of 10 per cent amino acids and 10 per cent glucose, one in the morning and one in the afternoon, and you can see, even though the total amount of nutrition was the same, the patient was in negative nitrogen balance because the two were not given together. Interestingly enough, you will note that glycosuria was absent when the two were given together; when they were given separately or when glucose was given alone, the loss of glucose in the urine was considerable. So I don't think anybody now would give amino acids and glucose separately. But I find that physicians still give amino acids and glucose in the morning and glucose alone in the afternoon. Glucose given in the afternoon will not help the utilization of amino acids given in the morning.

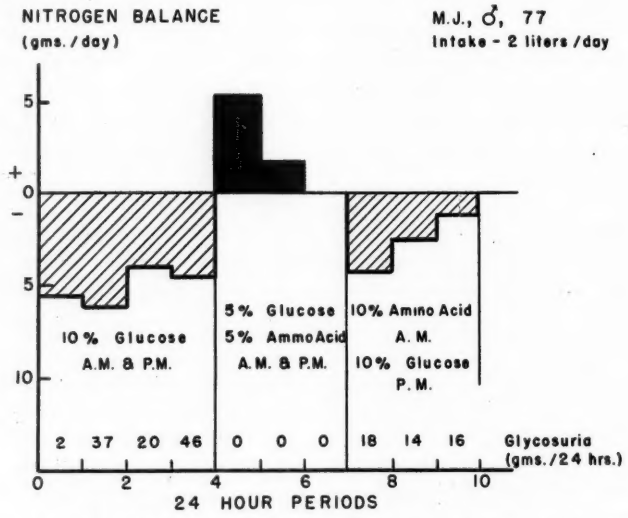

Fig. 4. A time factor in the administration of amino acids and glucose. (From Elman, R.: Surgical Care. Appleton-Century-Crofts, 1951.)

One really should then give the complete mixture both in the morning or in the afternoon, or preferably by continuous twenty-four-hour infusion with an indwelling catheter as described by Dr. Lowe this morning.

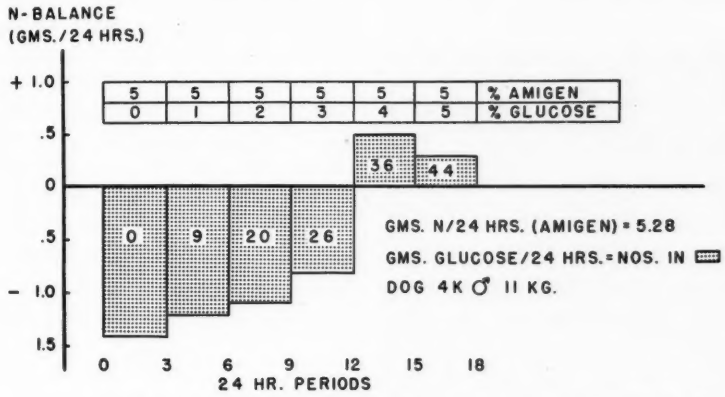

Fig. 5. The effect on nitrogen balance of adding increasing amounts of glucose to amino acids.

Of the several advantages of fructose over glucose, one is its better utilization in diabetics. Insulin apparently is not as necessary for the metabolism of fructose as it is for glucose. Another very interesting thing we have found was that there is no post-infusion hypoglycemia with fructose. In other words, if you give an infusion of glucose even to a normal individual or any other type of patient, the stimulus of the insulin production or whatever it may be that clears the blood of glucose, is so great that it continues after the infusion is ended. Sugar continues to be removed from the circulation and the blood level therefore drops to as low as 40 mg. per cent. With fructose this low post-infusion hypoglycemia does not occur.

Proportion of Amino Acids and Carbohydrate.—Our next studies deal with another factor in the utilization of amino acids, which is rather important and certainly interesting—"What proportion of amino acids and glucose shall one give?" In our first work we hit upon 5 per cent of each on the basis of an experiment which we never published, but I thought you would be interested in seeing. Nitrogen balances were measured in three-day periods in a dog (Fig. 5). During the first three days we gave 5 per cent amino acids and no glucose; nitrogen balance was negative. Then we added 1 per cent glucose and it became less, with 2 per cent it became still less, 3 per cent still less. When we got to 4 per cent positive balance followed. We didn't see any more improvement when the glucose was increased to 5 per cent so we went no further. But really this was a very simple yet incomplete experiment. We finally got around to doing a more adequate

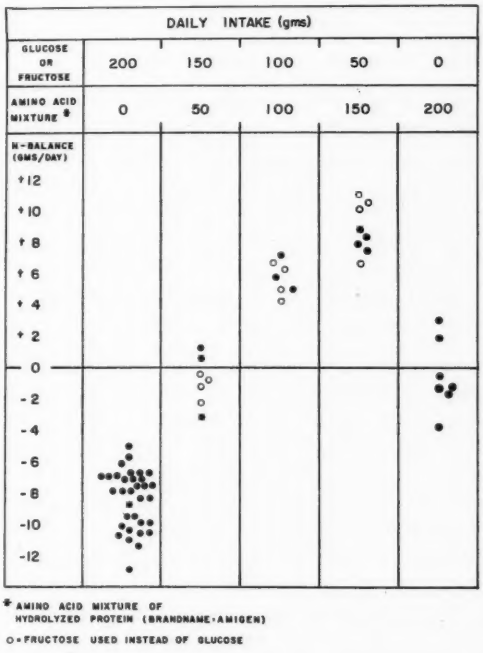

Fig. 6. Nitrogen balance on varying proportions of carbohydrates and amino acids. (From *Transactions of the American Surgical Association*, Cleveland, Ohio (April 27) 1954)

experiment in humans. We made a systematic study of 29 patients by giving daily infusions containing 200 grams but with varying proportions of amino acids and glucose.

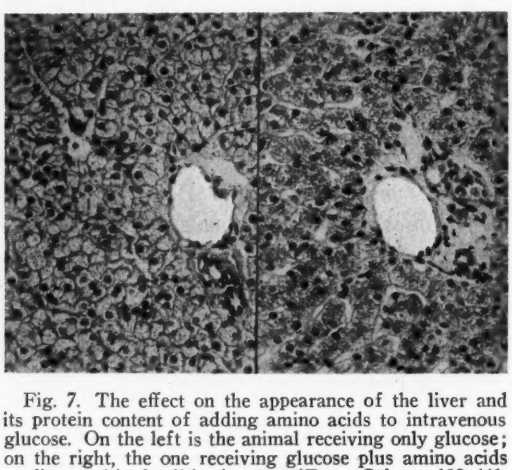

Fig. 7. The effect on the appearance of the liver and its protein content of adding amino acids to intravenous glucose. On the left is the animal receiving only glucose; on the right, the one receiving glucose plus amino acids as discussed in detail in the text. (From *Science,* 108:441, 1948.)

The results of this experiment are shown in Figure 6 in terms of nitrogen balance. When glucose or fructose was given alone, 200 grams with no amino acid mixture, all were in negative balance ranging from —12 grams up to about —5 or —6 grams per day which, of course, was what one would expect.

By contrast, when the intake contained no glucose or fructose at all, only amino acids, two of the patients were in positive nitrogen balance and even in the ones that were in negative nitrogen balance none were as much negative as the ones receiving glucose alone. So from that alone you would say if you are going to give a pure 10 per cent solution, in terms of nitrogen balance, you would be better off giving 10 per cent amino acids instead of 10 per cent glucose. Yet it is said that 10 per cent glucose is preferable to amino acids alone. These figures certainly would deny it. However, when you use a mixture, the figures are even more interesting. If you give 2½ per cent amino acids and 7½ per cent glucose, balance is around zero. If you give 5 per cent of each, it is between +4 and +8 grams per day, but the best nitrogen balance occurred when we gave 7½ per cent amino acids and 2½ per cent glucose or fructose. Actually the statistical difference in the latter two groups is not very great. But the data give confirmation of the fact that an equal mixture of amino acid and glucose really gives better nitrogen balance than 2½ per cent amino acids and 7½ per cent glucose.

Now I know that many of you perhaps have said that conclusions based on nitrogen balance are open to criticism. What we would like to know is whether these amino acids are actually utilized to build body tissue. A number of years ago we did an experiment which is very pertinent in this discussion. It is shown in Figure 7.

One group of dogs received amino acids and glucose and the other received glucose alone. Figure 7 shows the condition of the liver after two weeks of daily infusions. When glucose alone was given (photomicrograph on left), the liver is vacuolated, there is no stainable cytoplasm, the sinusoids are almost obliterated. This is what the pathologist actually calls hydroptic degeneration. This is a liver that contains a large amount of glycogen but has a very small content of protein, by analysis, about 2.8 per cent nitrogen. Next to it is a comparable section around a central vein in a similar experiment in which amino acids were substituted for part of the glucose. Note that the cytoplasm stains normally, the sinusoids are not crowded and actual chemical analysis showed that the nitrogen content was 3.3 rather than 2.8 grams per cent. In other words, here we have I think fairly good histological proof that amino acids are converted into liver protein and that glucose alone is not.

The next series of slides illustrate an important principle I would like to emphasize. The first data comes from the Rutgers group (J. Nut. 36:733, 1948) and represents percentage of nitrogen absorbed and utilized by the body. These are animal experiments. Note the different caloric intakes. The greatest amount of nitrogen absorbed, between 30 and 40 per cent, occurs when the dog got a high caloric intake. Note, however, that with a 50 per cent subcaloric intake, he was still utilizing 10 per cent of nitrogen whereas with no protein at all the figure would be zero.

The next two slides show similar findings from the work of Dr. Warren M. Cox. In this case protein synthesis was measured by actual analysis of nitrogen in the carcass of the animal as the caloric intake increased. Note that when glucose alone is given, there is no increase in the protein of the carcass, whereas on a 50 per cent subcaloric intake with protein there is a definite increase.

(Such an intake is analogous to the one we use clinically, namely 5 per cent amino acids, 5 per cent glucose, 2 liters a day plus vitamins which thus becomes an almost complete parenteral diet.) That a considerable amount of protein is laid down in the carcass illustrates again that you do not have to have full calories to get some good out of the protein that is added.

The next slide (not reproduced) shows a similar type of experiment—in this case based upon the weight gain of depleted animals given various mixtures of protein and carbohydrate. When there is no protein intake, of course they continue to lose weight. With full calories the weight gain is impressive, but note the gain on a 50 per cent subcaloric intake. They don't gain as much weight as they would on full calories, but they are certainly better off than with no protein at all.

Figure 8 illustrates this principle in a diagrammatic way. Each physician has the opportunity of giving a parenteral feeding mixture to his patient in any way he wishes and I find that by and large most patients receive 2 liters of 5 per cent glucose or 10 per cent glucose. Now if you give 5 per cent glucose, the average loss of nitrogen is about 6 grams per day. The patient will therefore be in 6 grams negative nitrogen balance. If you decide to give them more calories as 10 per cent glucose (you add 100 grams of glucose) you will find that he still puts out 6 grams of nitrogen and still has a —6 grams of nitrogen deficit. What you have done, then, with the added calories, obviously, is to spare tissue fat from which the body gets the rest of its energy. Since the body cannot exist without energy, our problem is to decide whether to give them exogenous energy or let them use the energy from their own body tissues. If they have to get energy from protein tissue, they lose protein, which is physiologically undesirable. But if they get calories from tissue fat, it is not physiologically undesirable; in fact, there are many of us in this room who would like to increase their physio-

HALF A LOAF IS BETTER THAN NONE.

Daily Intake	N. Output (grams)	N. Balance (grams)
1. Basic intake (2 L. 5% glucose)	6	- 6
2. Plus 100 grams glucose (2 L. 10% glucose)	6	- 6
3. Plus 100 grams amino acids (2 L. 5% glucose 5% amino acids)	15	- 2

Fig. 8. Decrease in negative nitrogen balance following the addition of amino acids. The table represents a theoretical calculation illustrating that added glucose does not necessarily influence negative nitrogen balance whereas added amino acids may.

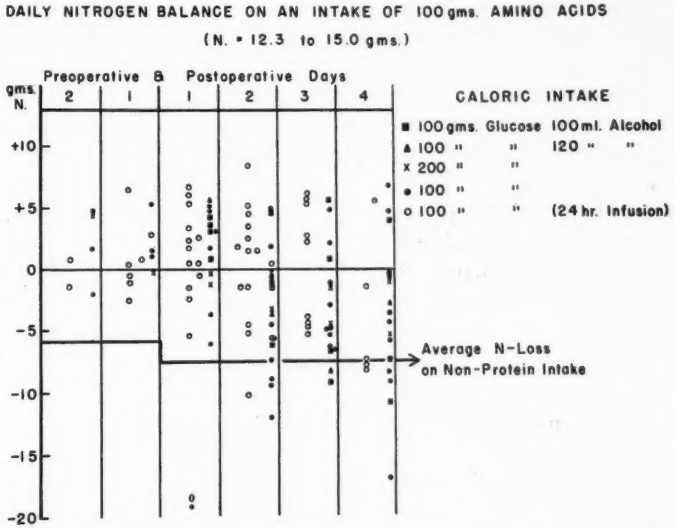

Fig. 9. Nitrogen balance before and after operation. The scattergraph represents specific data in a number of surgical patients undergoing major abdominal procedures and maintained on completely intravenous fluids for two preoperative and four postoperative days.

logical efficiency by getting rid of some of this adipose tissue.

What happens if, instead of adding 100 grams of extra glucose, we add 100 grams of amino acids. Now the output of nitrogen goes up which means that not all of the nitrogen given is utilized. But even under the worst circumstances you will get a reduction in the negative balance, say to —2 grams per day which is a saving of 4 grams of nitrogen. This doesn't make much difference in a well nourished patient and I won't quarrel about it. Moreover, it won't make any difference for one day or two days or three days, but the point is that these facts illustrate a principle. If protein is not added to the parenteral diet or if it is not added to the oral diet, the patient will be in more negative nitrogen balance than if you did add protein at any level of caloric intake. If you don't mind losing protein tissue, all right; but if you do, then you must add protein regardless of the method of administration and regardless of the state of nutrition. There is one exception. That is the well nourished patient during the first few days of the subcaloric intake.

Figure 9 is a scattergraph showing nitrogen balances before and after operation when amino acids were used. When we gave more calories, of course, they had better nitrogen balance as Dr. Rice and others have shown. I would like to point out that this line—this straight line across here—represents the average nitrogen loss which would have occurred if they had no protein intake. Actually, most, I would say 80 per cent, of the points were above that line and indeed many of these patients both before and after operation were in positive nitrogen balance. The worse nitrogen balance was this little spot down here (—23 grams a day) and I was a little disturbed about it until I looked up the data on the patient and found that this figure happened to occur in one who, unlike all the rest of them, did not get amino acids on that day, but simply got glucose alone.

In conclusion, I would like to say that my main theme is a very simple one—that food is necessary for life, for the sick just as it is for the healthy. By food I mean each of the known needed elements in the diet. Moreover, if you can't give all they need of any element, less than all is better than none at all.

I would also like to take this opportunity of expressing my thanks to the Hennepin County Medical Society and the Hennepin County Chapter of the American Academy of General Practice for this invitation to speak and, as a member of the audience, to all of the other speakers whose presentations I have so enjoyed hearing.

PEDIATRIC ELECTROLYTE PROBLEMS

(Continued from Page 20)

ing the first twenty-four hours, and 2,400 ml/M^2 thereafter. When patients are not dehydrated, use 1500 ml/M^2/25 hours. For initial therapy, do not give potassium-containing solutions. Use one third normal saline, 360 ml/M^2 administered in forty-five minutes. Most patients will void in forty-five minutes at this rate of delivery. If they do not void, change that rate of administration to 2,400 ml/M^2/24 hours, but do not use potassium-containing solutions until a patient voids.

I think that the data discussed summarize our present thinking about this problem. Much more could be said about details of management; however, in the last analysis each child has unique problems, demands compromises and improvisation, and the alert physician treats him as a law unto himself.

Discussion

DR. EDMUND FLINK: It has occurred to me that some of you might have been confused by the use of the word "normal solution" because of the fact that physiological salt solution or isotonic salt solution is sometimes erroneously called normal salt solution. Isotonic salt solution is neither physiological nor normal. Dr. Helmer was speaking in terms of the chemical definition, namely, an equivalent weight of a particular salt per liter of solution. Both Dr. Helmer and Dr. Darrow have indicated the utility and the clarity of the designation of electrolytes in terms of milliequivalents. This is just as reasonable as recording your personal assets in terms of dollars and cents rather than in terms of quantities of goods. It is just as easy to learn the normal values of these in milliequivalents as it was to learn the heterogeneous units of measurement.

I wish to re-emphasize Dr. Lowe's remarks about keeping information on patients who have fluid and electrolyte problems. It is vitally important to obtain daily weights of these patients and to keep a careful record of all intake and output. Although it is often difficult to keep a record of the output, this is very necessary in order to handle a complicated problem.

To enlarge a little bit on the arithmetic of the problem, I wish to remind you that the molecular weight of sodium chloride is 58; thus 5.8 grams of sodium chloride contain 100 milliequivalents. Nine grams of sodium chloride, as is present in an isotonic solution, contains 155 milliequivalents. Potassium chloride has a molecular weight of 74. The ampule which contains 40 milliequivalents, therefore, will have approximately 3 grams of potassium chloride.

While I am talking about the quantities of potassium chloride to be administered, I wish to call your attention to Dr. Darrow's remarks about the requirements of potassium. This fits in very well with our observations on patients with alkalosis of vomiting. Potassium must be administered in a quantity sufficient to replace the deficiency. We have come to the conclusion that it is necessary to administer from 120 to 160 milliequivalents of potassium per day (8.4-12.0 grams KCl) in order to get anywhere in the correction of a metabolic alkalosis. This amount fits very well with Dr. Darrow's figure of 3 milliequivalents per kilogram of body weight per day. This amount of potassium chloride would be required to correct a potassium depletion in a patient with pyloric obstruction. Inadequate amounts of potassium will tide the patient over for a short period of time but will not get at the basic difficulty, as Dr. Lowe has so clearly shown in the patient who had an orthopedic operation and developed a serious potassium deficiency.

I certainly think, as Dr. Lowe has mentioned, that wherever possible it is wise to administer fluids throughout a twenty-four-hour period when the patient is seriously depleted. In addition, it is well to put a polyethylene tube in the vein and thereby have a continuous infusion. I also wish to warn you of the fact that one must not administer a concentrated solution of potassium intravenously by syringe, although the concentration in the body is not very great, for the concentration in the coronary circulation could be lethal. Rapid administration of solutions of potassium chloride, therefore, must be considered to be dangerous.

Two tables Dr. Lowe showed may have been a little confusing because the electrolyte concentrations were different from those of Dr. Helmer's. Dr. Helmer showed the concentration of electrolytes in serum, whereas Dr. Lowe's table showed the concentration in the extracellular water. It must be remembered that the extracellular water has no protein, and therefore the concentration of chloride and sodium is slightly higher than that which is found in the serum.

QUESTION: Dr. Lowe, will not the alveolar wall of the lung sustain trauma from ether anesthesia on the first and second postoperative days and cause localization of fluid in the lungs resulting in pulmonary edema and atelectasis, if suction losses are replaced exactly? Apparently the idea is, can one give excessive amounts of sodium chloride in the first few days postoperatively? Dr. Lowe, will you open the discussion please?

DR. LOWE: The normal intake of potassium for the adult is about 4 grams, 100 milliequivalents. That is equivalent to approximately 8 grams of potassium chloride. We do not use normal saline in treating patients postoperatively. Our experience with one-third and one-fifth normal saline has indicated that we are entirely safe in giving the amounts of fluid which I indicated on the slides in the immediate postoperative period. In following the serum concentration of sodium, chloride and potassium in these cases, we have not found levels to occur which we thought were deleterious to the patient.

Dr. Calcagno of Buffalo has studied the glomerular filtration rate and renal plasma flow in postoperative children and found these to be normal. Dr. Ariel has found the same to be true in adults and furthermore has failed to demonstrate a predictable change in the ability of the kidney to handle sodium and chloride postoperatively, although there is a tendency to retain sodium when normal saline is given.

Dr. Darrow, by his question, has given me a chance to mention some other things that I left out. I would say that the Number 1 rule for adequate surgical management of children is co-operation between pediatrician and surgeon. Nothing prejudices good surgery as seriously as a poorly prepared patient or one whose postoperative management is inadequate. We are willing to

watch a patient with pyloric stenosis for as long as five or six days before operation in order to get him into shape and we have followed patients with an intussusception as long as eighteen to twenty hours in an effort to try to get them in better shape for surgery, knowing full well that a resection might be necessary because of the delay. If a seriously ill patient is not in fairly adequate electrolyte balance, he will not survive the operation.

QUESTION: Dr. Lowe, if one chooses the sodium content of colostrum as representing the normal sodium intake in an infant, would you give less than this normal amount after operation on the basis that you might anticipate some sodium retention associated with the stress response? Secondly, please discuss your two polyionic solutions. Are they available?

DR. LOWE: I would say that dilute solutions which have a concentration of electrolyte in the range of that of colostrum would be acceptable for replacement fluid for a newborn child who has required an operation. The volume used should be similar to that which might be taken by mouth in a similar child without operation. With the use of such solutions in probably over a hundred babies, we have never seen postoperative edema unless there were complications, such as sepsis, which of their own accord would cause edema. We have seen it in newborn babies, however, when we have used solutions which contain 40 to 60 milliequivalents per liter. It is my impression, and I think there is experimental evidence to substantiate this impression, that the newborn infant is remarkably capable of handling water and is very capable of controlling his electrolyte excretion.

DR. FLINK: It is always worthwhile to look at a problem in more than one way, and to express it in slightly different words. I wish to emphasize again the utility of expressing electrolyte concentration in terms of milliequivalents because of the clarity and the understanding that is permitted.

Dr. Helmer's illustration of the use of chloride and bicarbonate (CO_2) concentrations to estimate approximately the total electrolyte concentration in the serum is just one example. It would be impossible to get any idea of that if one reported CO_2 in terms of volumes per cent and chloride in terms of milligrams per cent. Some laboratories report chlorides as milligrams of chloride ions and others report it as milligrams of sodium chloride. It is also useful to think of the administration of electrolytes in terms of milliequivalents rather than grams. At the present time, the polyionic solutions that are available commercially have on their labels the number of milliequivalents that are available in each 100 milliliters. Potassium chloride ampuls designed to be added to parenteral fluids are labeled as 20 or 40 milliequivalents.

QUESTION: Dr. Helmer, is calcium completely dissociated in the blood, and if so, is it therefore legitimate to express it in terms of milliequivalents per liter?

DR. HELMER: About one-half of the calcium is bound to protein. Since protein can be expressed in milliequivalents on the basis of its cation binding capacity, I think it is legitimate to express calcium concentration in milliequivalents.

QUESTION: Dr. Helmer, will you review the laboratory steps which are necessary to evaluate the sodium content of the serum when a photoelectrometer is not available? You gave a formula and we would like to have it explained to us.

DR. HELMER: Add the value of the CO_2 combining power (bicarbonate concentration), the normal of which is 27 mqs., to the value of the chloride concentration, the normal of which is 103 mqs. From these you obtain a value of 130 mes. per liter. Then if you subtract that, 130, from the 142, the normal sodium value, you will obtain a difference of 12. On that basis, if you add the chloride value plus the bicarbonate value and add 12, you can estimate the sodium concentration.

QUESTION: Dr. Helmer, if the sum of the CO_2 and chloride is above the normal, can this be interpreted as a significant hypernatremia?

DR. HELMER: Yes, you can expect to have a hypernatremia.

QUESTION: Dr. Helmer, what happens to the value of the sum of CO_2 and chlorides in metabolic acidosis or uremia?

DR. HELMER: In metabolic acidosis or uremia this calculation will not be valid. In metabolic acidosis there is an accumulation of organic acids and in uremia there is an accumulation of phosphates or sulfates along with elevation of the other anions.

QUESTION: Dr. Darrow, in a patient with prolonged loss of hydrochloric acid as in a case of an obstructed duodenal ulcer, isn't it probable that an actual chloride deficiency supervenes?

DR. DARROW: I'm sure that it does sometimes, but ordinarily I think most of our chronic alkaloses are intermittent in the sense of a loss of chloride if water does get into the body, and I think that if large amounts of chloride are actually lost from the body in the sense of an absolute deficit, you will find that the concentrations of sodium in the serum are low. I know that theoretically it can occur without that, but I think practically it will be usually with a low sodium concentration.

DR. FLINK: I wish to emphasize again what Dr. Seldin has mentioned, namely, the importance of recognizing the possibility of an electrolyte imbalance when a patient fails to respond to a mercurial diuretic. When this occurs, one should investigate the electrolyte status in an effort to determine the reasons for that failure to respond.

DISCUSSION

QUESTION: Dr. Seldin, can you comment on the prognosis of patients with a low salt syndrome which is refractory to therapy?

DR. SELDIN: Patients with a low salt syndrome are presumably patients who have a low concentration of sodium in the serum and who are edematous at the same time. I think one can distinguish two types of a low salt syndrome. In one type, the low salt syndrome develops chronically without any acute onset. A cardiac patient will retain water in excess of salt, thereby leading to a severe hyponatremia. Under those circumstances, one can correct the hyponatremia with hypertonic saline but almost invariably water will again be retained, diluting the sodium down to its previous values. The correction of chronic dilution hyponatremia in congestive heart failure often eventuates in no clinical improvement.

In contrast to this, there is the problem of acute dilution hyponatremia as in the cardiac who also begins to retain excessive amounts of water. Under these circumstances, the administration of hypertonic saline may be life-saving. These states in heart failure should be contrasted with similar states in nephrosis or cirrhosis. Chronic dilution hyponatremia as low as 120 milliequivalents may be tolerated by the cirrhotic patient with surprisingly little ill effect. There is, however, a form of acute dilution hyponatremia in cirrhosis which demands immediate attention. This develops under circumstances where a cirrhotic develops a paracentesis while he is on a salt-free diet. Here water is retained, but no salt is available. Severe hyponatremia supervenes, transudation occurs into the cirrhotic sac and as a consequence of this the blood volume shrinks, peripheral vascular collapse occurs and a lethal outcome may follow. Cirrhotics who are tapped completely of their ascitic fluid are in a precarious state when they are on a salt-free diet and should they become drowsy, disoriented, and so forth, hyponatremia should be suspected and hypertonic saline administered.

Dr. Darrow has raised the question of the concentration of the replacement solution. This should be either 3 or 5 per cent saline in the cirrhotic. Where congestive heart failure is not a problem, 5 per cent saline can be given in amounts which can be estimated from the sum of the CO_2 and the chloride or directly from the concentration of serum sodium. In a cardiac patient where the problem of a massive intravenous load is a formidable one, one should give the solutions slowly in divided doses.

QUESTION: Dr. Seldin, what is the effect of potassium deficiency on the action of digitalis in the treatment of congestive heart failure?

DR. SELDIN: Potassium seems linked in some manner with the action of digitalis in a reciprocal fashion. In order to potentiate a response to digitalis, potassium deficiency must be corrected.

Fluid and Electrolyte Requirements of the Surgical Patient as Influenced by the Post-Traumatic Response

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THE TITLE of this paper is particularly timely because the body's response to trauma—the so-called alarm reaction or reaction to stress—now dominates surgical thinking, especially in regard to defining it and to devising repair solutions to counteract the deleterious effects of this reaction. No one can deny the importance of this reaction but, as so frequently occurs in surgical thinking, certain styles prevail for a given period and, as with ladies' hats, change frequently causing yesterday's style to be shunned and discarded. Today emphasis is upon reaction to stress and the literature abounds with attempts to explain all postoperative phenomena as stress reactions. Throughout the history of surgery, each era has had a particular feature which it has emphasized as being the all-important one for the safe conduct of a patient through an operation. At first when the surgeon was a mere tissue technician, no special efforts were made as regards preoperative and postoperative care. Were it not for the results of infection, it is highly probable that many of these surgical patients would have survived because their homeostatic mechanisms, developed as a result of evolutionary improvements, would have functioned to help convalescence and restore health.

With the emphasis placed on the importance of saline solutions by O'Shaughnessy in 1831, an era prevailed in which saline administration was promiscuously practiced. Coller and Maddock were great exponents of the saline regime for surgical patients and contributed greatly to a better understanding of crystalloid balance in patients undergoing operation.

Over-enthusiastic administration of saline solution by many surgeons was contributory to further lines of thought and practice in treating the patient postoperatively. In 1936, George Hoyt Whipple focused attention upon the importance of protein metabolism and the serious consequences of hypoproteinemia. One of these consequences, edema, was markedly aggravated by the administration of saline. This brought attention to the necessity of supplying proteins to the surgical patient, and some of the greatest advances in this field were made by Elman who carefully studied nitrogen balance in the surgical patient and presented methods of supplying proteins, including the intravenous administration of amino acid mixtures.

The dangers of saline infusions caused certain surgeons to avoid completely any crystalloids during the immediate postoperative period. Among these was Wangensteen, who freely administered ionic-free water postoperatively. This afforded me an opportunity to study the effects of water administered to the surgical patient. A rather high incidence of water intoxication resulted which was not appreciated as such, and a number of postoperative patients suffering convulsions and coma were, therefore, diagnosed as having cerebral vascular accidents.

The recent brilliant studies of Darrow emphasized the important role of the potassium ion in the maintenance of a normal electrolyte structure in patients, demonstrated its defect in infants suffering from diarrhea, and showed that the administration of this ion would at times be lifesaving. He and his associates further developed an explanation of the intermediary metabolic reactions between the various ionic compartments of the organism. It was but a short step to apply these data to certain complications suffered by postoperative patients which resist the ordinary methods of treatment. In this respect I must admit with a certain amount of embarrassment that in a paper written by myself in conjunction with Doctors Abels, Pack, and Rhoads, we described a form of hypochloremia which resisted sodium chloride administration. Under the influence of the "protein age," we attributed the fundamental defect to hypoproteinemia. In all probability we were

describing hypokalemia, for the clinical and chemical studies we described in that paper are very similar to those which are the result of potassium deficiency.

With this introduction, I should like to describe some of the reactions which occur in the patient subjected to an operation in an attempt to identify the nature of the ensuing developments.

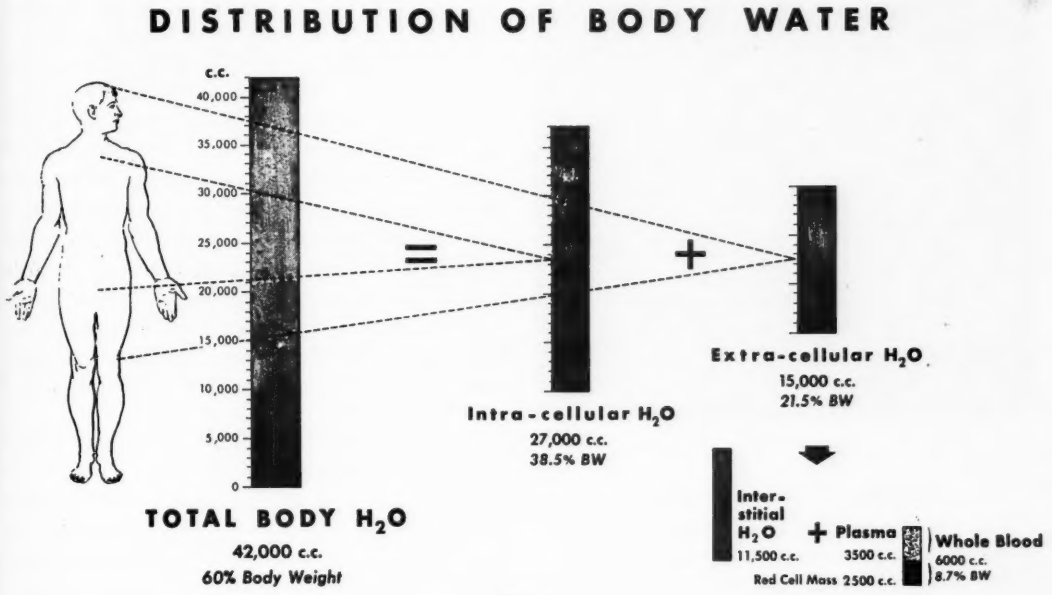

Fig. 1.

Numerous other factors compete for high priority as regards their importance to the postsurgical patient. Among these are vitamins, blood, plasma and plasma expanders, early ambulation, and others. Doctor Carl Rice and his associates deserve credit for focusing attention upon the caloric requirements of the surgical patient, indicating the substandard caloric content of most postoperative hospital regimes, and devising methods of supplying calories, including the use of intravenous alcohol solutions combined with other calorie-containing ingredients.

In reviewing the physiologic aspects of surgical convalescence, it becomes apparent that no single feature is omni-important. Rather, each contributes a necessary link in the maintenance of homeostasis, and a deficiency of any one substance produces a break in the chain of metabolic reactions, the clinical sequelae of which can be disastrous. Nevertheless, during each of the ages certain of the preceding factors dominated surgical thought. Each was considered the all-important item by certain physicians, and heated arguments were not infrequent at medical meetings.

TABLE I.
CLASSIFICATION OF EDEMA AND DEHYDRATION

Bound Water (Osmotically Inactive)	Osmotically Active Water	
	Extracellular Compartment	Intracellular Compartment
1. After injection of certain hormones (estrogens).	1. Edema	Normal
2. Three and one-half grams of water deposited with each gram of protein.	2. Edema	Dehydration
3. Two ± grams of water deposited with each gram of glycogen. (Fat is deposited dry.)	3. Edema	Edema
	4. Dehydration	Normal
	5. Dehydration	Dehydration
	6. Dehydration	Edema
	7. Normal	Edema
	8. Normal	Dehydration

In order to interpret the effects of surgery upon the patient we must first appraise the condition of the patient as he comes to operation. It is not infrequent for the patient to be in a deplorable state of fluid and electrolyte balance and to come to the operating table in that particular state. Then, as a result of the operation, another insult is added to the metabolic trauma that the patient has suffered and the sum total is interpreted as a result of surgery. A few of these alterations found in patients coming to surgery are expressed in the first few figures.

Figure 1 is an expression of the distribution

of water, indicating that water constitutes about 60 per cent of the body weight divided into intracellular and extracellular components. We must think not only of loss or gain of water but also of the distribution of the water within the body.

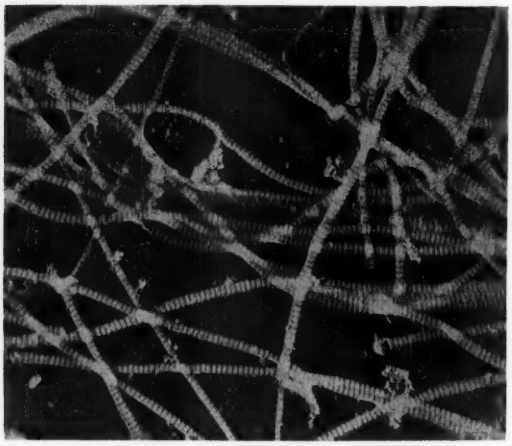

Fig. 2.

Table I demonstrates the various kinds of abnormalities of water distribution that can be produced. The administration of so-called normal saline causes extracellular edema; giving hypertonic saline produces extracellular edema with an intracellular dehydration. We observed extracellular dehydration and intracellular edema in our patients who developed hypochloremia as a result of withdrawing gastric juice. If saline solution is given rapidly to a patient in hypochloremic alkalosis before he has a chance to adjust his mechanism, one of the worst types of edema, namely, intracellular and extracellular edema, results.

We have become accustomed to using the term "extracellular edema" or the "extracellular space" very loosely. Figure 2 shows the electron microscopic appearance of the extracellular space. We see the various fibers and the matrix of the space. We must recognize that this is not a space. It is not a simple space in which fluid goes in and out, but it is an organ which has its special form, structure, and function. Thus we must visualize the body as consisting of two types of circulation, (1) the blood circulation as we know it, and (2) the circulation of the extracellular space. We must also think of the response of the patient to operation in terms of (a) response to the external environment, i.e., abnormal losses and abnormal gains of the various waters and electrolytes; and (b) internal balance, i.e., the shifts which occur between the cell itself and this extracellular space. When alterations occur in this particular space, they have direct reflections upon the cell. We must always bear in mind that any substance given to treat an intracellular defect must first be given into this extracellular space. Ingested or injected fluids and electrolytes must be deposited here, exert their influence here. This influence is then transmitted to the cell.

Table II shows some of the changes produced by water and salt loss preoperatively which, if unrecognized, will result in operating upon a metabolically imbalanced patient. In patients who lose gastric fluid, there is a marked difference between those with ulcers who have a hyperacidity of their gastric contents and those with gastric cancer who usually have a gastric anacidity. The fluid withdrawn from these patients in a period of three to five days of constant gastric lavage contained 629 mEq. of chloride in patients with hyperacidity and 369 mEq. of chloride in the patients with anacidity. Sodium loss was less in the first group in comparison to sodium loss in patients with anacidity. There was a significant amount of potassium withdrawn. Thus, in patients with hyperacidity the gastric aspirate contained a marked excess of chloride in relation to sodium, whereas in patients with gastric anacidity this excess was much less and the loss was one of almost a total salt, sodium and chloride.

The indicated changes are reflected in the

TABLE II. THE CONTENT OF CHLORIDE, SODIUM, AND POTASSIUM OF THE FLUID WITHDRAWN BY GASTRIC ASPIRATION IN PATIENTS WITH GASTRIC CARCINOMA

Case No. Patient	Quantity of Gastric Fluid Aspirated, Liters	No. of Days of Withdrawal	Chloride		Sodium		Potassium	
			mEq./l.	Total Amount Aspirated, mEq.	mEq./l.	Total Amount Aspirated, mEq.	mEq./l.	Total Amount Aspirated, mEq.
1—L.G.	3.5	6	85	297	80	280	10	35
2—C.V.	5.4	4	96	518	92	487	12	65
3—B.B.	4.5	5	76	342	74	333	15	67
4—J.C.	5.3	5	62	329	59	323	17	90
5—M.L.	5.5	4	65	357	60	330	8	44

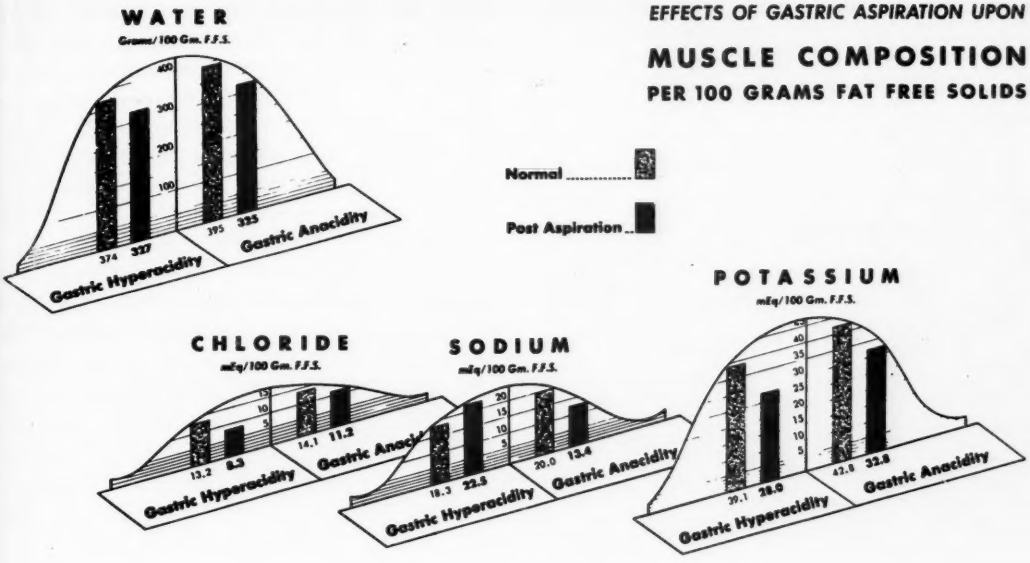
EFFECTS OF GASTRIC ASPIRATION UPON
MUSCLE COMPOSITION
PER 100 GRAMS FAT FREE SOLIDS
Normal
Post Aspiration
WATER
Grams/100 Gm. F.F.S.
374
327
395
325
Gastric Hyperacidity
Gastric Anacidity
CHLORIDE
mEq/100 Gm. F.F.S.
13.2
8.3
14.1
11.2
SODIUM
mEq/100 Gm. F.F.S.
18.3
22.5
20.0
13.4
POTASSIUM
mEq/100 Gm. F.F.S.
29.1
28.0
42.8
32.8

Fig. 3.

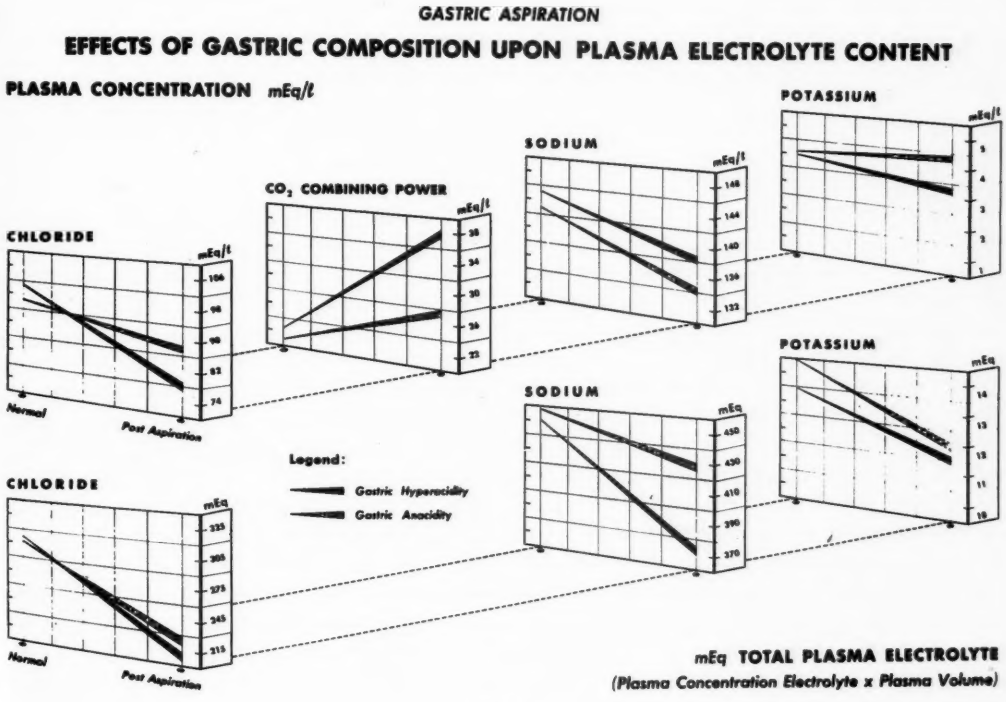
GASTRIC ASPIRATION
EFFECTS OF GASTRIC COMPOSITION UPON PLASMA ELECTROLYTE CONTENT
PLASMA CONCENTRATION mEq/l
CHLORIDE
CO2 COMBINING POWER
SODIUM
POTASSIUM
Normal
Post Aspiration
Legend:
Gastric Hyperacidity
Gastric Anacidity
mEq TOTAL PLASMA ELECTROLYTE
(Plasma Concentration Electrolyte x Plasma Volume)

Fig. 4.

TABLE III. AVERAGE ALTERATIONS IN SERUM CONCENTRATION OF HEMOGLOBIN, PROTEIN, UREA NITROGEN AND CERTAIN ELECTROLYTES DURING ABDOMINAL OPERATIONS

	Pre-operative	Post-operative	Next A. M.
Hemoglobin (Gm. %)	14.9	14.4	14.2
Hematocrit (%)	46.3	47.6	45.3
Total Serum Protein (Gm. %)	7.0	6.6	9.9
Blood Urea Nitrogen (mg. %)	9.9	17.3	11.9
Serum Electrolytes (mEq./l.):			
Chloride	97.1	101.9	90.9
CO_2 Combining Power	25.6	22.5	25.3
Sodium	142.2	148.2	139.0
Potassium	4.3	4.2	4.7

during intraabdominal operations is hindered by variables which are difficult to control. Such factors as anesthesia, the trauma of operation *per se*, and the body's reaction to the operation, each contribute a part in the overall picture of the metabolic response to the alterations incident to intraabdominal operative intervention. In addition, the administration of blood and other fluids during the operation further complicates the picture.

The following data were obtained by measuring metabolic responses to intraabdominal operations performed during warm summer months. Only

TABLE IV. ALTERATIONS IN SODIUM BALANCE OF PATIENTS DURING ABDOMINAL OPERATIONS

	Pre-operative	Post-operative	Balance	Next A.M.	Balance
Plasma Sodium, mEq./l.	142	148	+6	139	−3
Total Circulating Sodium, mEq.	440	385	−55	431	−9
Total Interstitial Sodium, mEq.	1944	2055	+111	2129	+75
	During Operation				
Urinary Excretion of Sodium, mEq.	28	66			

muscle biopsies (Fig. 3). I am grateful to Dr. Cooke of Dr. Darrow's laboratory for assistance in these calculations. We see here the marked increase in the intracellular sodium in patients with the gastric hyperacidity, and in patients with anacidity a loss of sodium.

Figure 4 shows the changes in the plasma concentrations of these two groups of patients. In the group of patients with gastric hyperacidity the chlorides dropped markedly, the CO_2 combining power rose, sodium fell, and potassium decreased slightly. Those with gastric anacidity had similar changes, but not as marked, and I emphasize this because the loss of the total salt may produce metabolic alterations that will not be reflected in plasma concentrations. In short, the loss of chloride over sodium will produce a typical hypochloremic alkalosis; a loss of the total salt will result in a marked diminution of all water and salt and the patient may not show the typical hypochloremic alkalosis we see when chloride alone is lost. Therefore, great care must be exercised in judging the plasma values of patients with gastric cancer.

The effects of the operation upon the metabolic status of the patient will dictate the quantities and types of repair solutions to be given during the operation and during the postoperative period. The study of metabolic alterations which occur

relatively small amounts of glucose in distilled water were administered to the patients during the operative procedures. The values referred to as operative losses indicate amounts lost during the actual operation; those listed as postoperative losses indicate losses from the completion of the operation until the following morning. (Tables III and IV).

There are two phases of the body's reaction to an operative procedure. The first consists of the balance between the individual and his external environment, and the second the alterations of balance between the cells and their environment (the extracellular compartment).

Balance Between the Individual and His External Environment.—This consists of a negative balance of water, certain electrolytes, and blood. The quantity of water lost varies in different individuals and in different surroundings, depending upon the conditions prevailing at the time of operation. Thus, in the warm summer months under heavy operative drapes, the individual loses significant quantities of water (two to four liters).

Contrary to the belief of many, urine output continues, sometimes in significant amounts, in certain patients during an operative procedure and during the immediate postoperative period. Although a number of individuals will manifest evi-

TABLE V. EFFECTS OF ABDOMINAL OPERATION UPON TOTAL BODY WATER, PLASMA VOLUME, RED CELL MASS AND INTERSTITIAL VOLUME
Average Values

	Pre-operative	Post-operative	Next A. M.
Total Body Water—D_2O (liters)	36.3	35.1	36.0
Plasma Volume (liters)	3.1	2.6	3.1
Red Cell Mass (liters)	2.6	2.3	2.6
Interstitial Volume (liters)	13.5	13.7	15.1

dence of water retention during the immediate postoperative period, this situation does not prevail for all patients, and certain individuals will excrete large quantities of urine. The reason why some patients will continue to excrete urine and others will not remains enigmatic.

It has been demonstrated that there is no significant kidney damage during operation as determined by measurements of renal clearance. The average renal plasma flow, renal blood flow, glomerular filtration and tubular absorption were not significantly affected during the abdominal operative procedures. These findings are summarized in Figure 5. If the operative trauma is great, and if anoxia and hypotension occur, renal damage may occur and contribute to oliguria. However, in most surgical patients it must be assumed that some extrarenal mechanism functions to cause water retention in those patients who receive adequate quantities of water, but who retain that water postoperatively. It would be erroneous to assume that water is retained by all individuals and therefore that water should be withheld postoperatively. It would be equally erroneous to feel that for those patients who manifest evidence of water retention, a greater quantity of urine can be produced by the liberal administration of water. The amount of water given to an individual postoperatively should depend upon the amount lost during the operation and during the postoperative period, which varies from individual to individual.

It is difficult to measure the quantity of water lost during the operation. A rough correlation exists when three methods of estimating total fluid loss are compared. Total body water as measured by deuterium dilution decreased by an average of 1.2 liters in a series of patients subjected to intraabdominal operations. Body weight decreased an average of 0.9 Kg. A small portion of this loss was accounted for by the resected specimen in some instances. A positive water balance of 105 ml. was noted during the operation when fluid intake and urine output were measured. An unmeasured quantity of water was lost by perspiration. Since each of these measure-

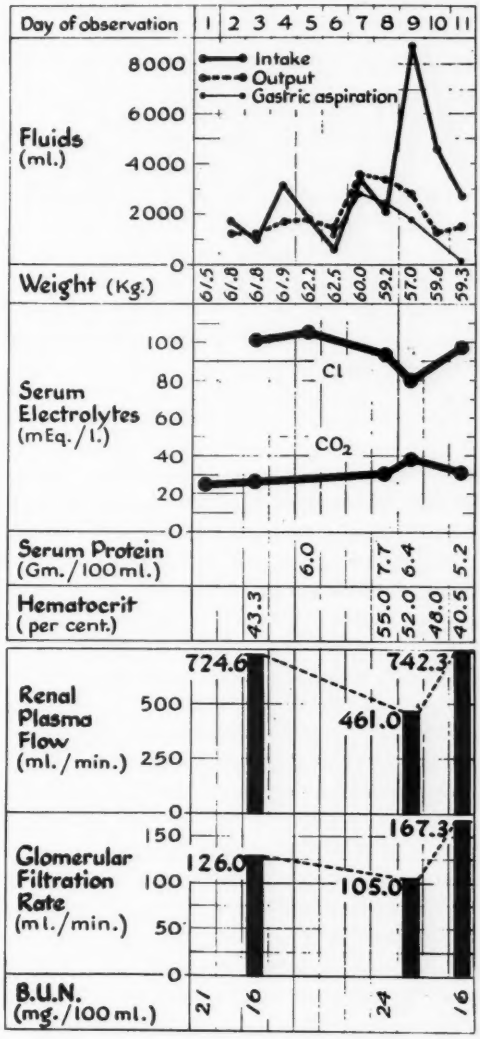

Fig. 5.

ments has an inherent factor of error, it may be assumed as a practical guide that approximately one liter of body water is lost during the three to six hours for intraabdominal operative procedures without undue trauma. There was an average loss of 300 ml. of red cell mass (Table V), which is equivalent to approximately 650 ml. of whole blood lost, or a plasma loss of 350 ml. (computed on the basis of the preoperative hematocrit level).

TABLE VI. AVERAGE URINARY EXCRETION OF ELECTROLYTES DURING ABDOMINAL OPERATIONS

	During Operation	Postoperative
Chloride (mEq.)	32	67
Sodium (mEq.)	28	66
Potassium (mEq.)	16	67
Nitrogen (grams)	1.4	8.7
K:N Ratio	13:1	8:1

Interstitial Fluid. Such wide fluctuations occur in the postoperative values for the interstitial spaces as measured by the sodium thiocyanate method that it must be concluded that the method is unreliable. It must thus be assumed that an unknown quantity of water was lost from the interstitial spaces and the remainder from within the cells. The urinary potassium lends support to this supposition as does the decrease in muscle water noted postoperatively on analysis of muscle tissue.

Electrolyte Loss During Operation.—A rather close correlation exists between chloride and sodium excretion, 32 mEq. of chloride and 28 mEq. of sodium having been excreted during the intra-abdominal operations. During this same period 16 mEq. of potassium was excreted. The postoperative urinary electrolytes of 67 mEq. of chloride, 66 mEq. of sodium and 67 mEq. of potassium undoubtedly represent excretory manifestations of trauma, although a slight amount could conceivably be accounted for by the 800 ml. of whole blood administered during this period (Table VI).

There does not appear to be any correlation between the total volume of urine and the amount of electrolytes excreted. It would thus appear that the excretion of electrolytes is not dependent upon the same factors which influence the water excretory mechanism. Thus one individual may produce a great deal of ion-poor urine while another may produce a small quantity of urine heavily laden with electrolytes.

Nitrogen Excretion.—Protein loss was manifested by excretion of 1.4 gm. of nitrogen during the operation which is equivalent, if all this nitrogen represents protoplasmic breakdown, to 46 gm. of tissue (Lusk's coefficient: 1 gm. N = 33 gm. of whole tissue), and during the day postoperatively 8.7 gm. of nitrogen was excreted, representing 287 gm. of tissue destroyed if all the urinary nitrogen is the end product of tissue catabolism.

All of the above described alterations reflect changes between the individual and his external environment. They probably represent the effects of the operative trauma upon the organism as well as a reaction of the organism to the stress— the alarm state. In addition to changes between the patient and his environment (alterations in balance), internal changes also occur, i. e., alterations between the cell and its environment—the extracellular space. These internal alterations are indicated by the marked change in the total circulating plasma protein with an egress of the protein from the plasma during the operative procedure and by changes in permeability of the cell membrane to chloride and sodium in certain instances.

This shift of electrolytes and proteins in and out of the plasma in answer to metabolic demands demonstrates some of the reactions to the alarm state. Whether any replacement therapy is indicated for these shifts is not known. The data further demonstrates the fallacy of utilizing serum concentration of various metabolites exclusively as criteria for replacement therapy.

Thus a patient may lose a small amount of sodium and chloride in the urine during an operation and the immediate postoperative period, but as the result of metabolic stress there may be a shift of the sodium and chloride out of the plasma into the interstitial spaces, inducing a decrease in the plasma content of these electrolytes. If one is guided exclusively by concentration values of the serum, one would be tempted to administer quantities of sodium and chloride sufficient to bring the value to normal. Although the exact method of coping with this abnormal shift is not known, it is believed that the excess administration of saline solution would be detrimental in such instances.

The adrenal response to the stress of a surgical operation will favor the excretion of potassium and nitrogen and retention of sodium and chloride. If an excessive response occurs which is further complicated by administration of sodium chloride solutions, abnormal retention of these electrolytes may become clinically dangerous. Moore and Ball have ascertained that an initial response to an operation (six day period) results in the normal release of 875 mg. cortisone, 10 mg. percorten and 300 cc. escharten.

Other factors which must be considered in the

overall appraisal of the effects of surgical intervention upon body metabolism are the quantities of energy used during an operative procedure and manifested by utilization of body carbohydrate and fat. A previous study in which the effects of operation upon liver fat and glycogen were measured in liver biopsy specimens taken preoperatively and postoperatively demonstrated an average loss of 2 gm. per cent hepatic glycogen. This amounted to a decrease of 45 per cent of the total hepatic glycogen, and in some cases the hepatic glycogen decreased 50 and 75 per cent below the preoperative level. There was also an increase of hepatic lipids during an intraabdominal operation, sometimes to rather large amounts.

Therapeutic Applications

The demonstration of certain defects which develop as a result of intraabdominal operations with a decrement of water, blood, electrolytes and nitrogen, some of which have been quantitatively measured for this study, indicates the quantity and type of repair solutions which should be administered during the operative and postoperative periods.

Water.—The observation that an average loss of one liter of fluid occurred during operation suggests that this quantity of fluid administered during an intraabdominal operative procedure should be well tolerated. The fluid loss, however, can be much greater, especially under surgical sheets during hot summer months, during which time the patients' temperatures have been noted to rise to 102 to 104 degrees (Fahrenheit). In such instances larger quantities of fluid are indicated.

It is impossible to generalize concerning the quantity of water to be administered. Certain surgical patients will develop an abnormal retention of administered water with an associated oliguria. In such patients water must be given cautiously; otherwise symptoms of water intoxication will develop. Because of this phenomenon, some surgeons have cautioned against fluid administration to patients during the operative and immediate postoperative period under the mistaken belief that all surgical patients retain water. This concept is in error. The ability of the surgical patient to excrete water or to retain it abnormally is an individual characteristic and must be evaluated for each patient.

Blood.—In a group of patients investigated by the author, average blood loss as determined by alterations in plasma volume and red cell mass, amounted to 650 ml. of which 300 ml. were red cell mass and 350 ml. plasma. These alterations are greater than the blood loss determined by extracorporeal methods (weighing sponges, etc.). The maintenance of an adequate blood volume is one of the greatest essentials of surgical practice, and it is felt that a minimum of 500 ml. of whole blood would be indicated in these patients during the operative seance.

There is a prevalent tendency to administer too much blood during operation. The most frequent guide is the patient's blood pressure, and any drop regardless of cause is considered a signal for continued blood administration. This is harmful and we have seen patients develop surgical polycythemia from such a practice. There is no good method of determining blood volume serially during an operation, hence caution must be exercised against the prevalent policy of promiscuous administration of blood. A mild vasoconstrictor to combat vasodilation, the use of plasma expanders, and gentle handling of tissue will reduce the necessity for administration of large quantities of blood.

Electrolyte Replacement.—Sodium, chloride and potassium are excreted during the operative procedure (32, 28 and 16 mEq. respectively) and during the immediate postoperative period (an average of 67 mEq. for each ion). Although the loss of this quantity of electrolytes should in itself not hamper convalescence, it is felt, nevertheless, that every effort should be made to maintain the preoperative balance, and replacement therapy should begin at the time of operation. If this is done electrolytes lost during the stress of the operation will be replenished. A dilute, polyionic solution such as described by Fox, et al., which contains 140 mEq./l of sodium, 103 mEq./l of chloride, 10 mEq./l of potassium, 55 mEq./l of bicarbonate, and small amounts of calcium and magnesium, would seem to be indicated. The administration of an electrolyte solution would also serve to buffer against the convulsions and coma of water intoxication which would occur if an excess of ionic-free fluid were administered and retained. One liter of this solution administered postoperatively would replenish the sodium and chloride losses as measured in this

study. The potassium decrement would not be significant, provided potassium replacement were instituted within four to five days after operation.

Fear of administering electrolytes to patients during the immediate postoperative period grips certain surgeons as the result of a preceding era when large quantities of 0.9 per cent sodium chloride were routinely administered to all patients postoperatively. Intelligent administration of electrolytes to replace those lost during operation is a more physiologic practice than fear and avoidance of these ions during and immediately after operation. Our study indicates that an estimate of electrolytes lost is a far safer indication for replacement therapy than serum concentrations of the electrolytes. In fact, abnormally low serum levels may ensue because of an abnormal distribution of the available electrolytes, and one should never strive heroically to raise a subnormal serum value to a so-called normal level by administration of massive quantities of repair solutions.

Nitrogen.—The loss of 1.4 gm. of nitrogen during the operative procedure and 8.7 gm. during the immediate postoperative period is not considered clinically serious, and it is felt that it does not warrant any immediate replacement therapy. A healthy convalescence with oral intake of protein foodstuffs will adequately replenish this loss. The plasma protein concentrations cannot be used as an index for protein replacement therapy because a large quantity of protein is mobilized from the plasma in answer to the metabolic demands of stress. In addition, the hydrodynamics of the plasma will mask the true plasma protein content.

Internal Balance.—A number of changes occur during an operation which reflect differences in distribution of certain metabolites. Such changes as the emigration of protein from the plasma or the abnormal ingress of sodium and chloride into the cells in certain patients reflect little understood responses of the organism to trauma, and nothing is known as to what therapeutic attempt is indicated if any.

Energy.—The expenditure of energy with the utilization of carbohydrates and fats during an operation demands caloric replacement. The body can withstand this short period of negative energy balance provided it does not progress over a prolonged period.

Postoperative Care

The patient immediately after an operation must be regarded as a traumatized individual in whom three sets of responses are occurring: (1) those responses which are the direct result of the injury to the organism, (2) normal responses by the organism in reaction to the traumatizing actions, and (3) abnormal responses due to the inability of the individual to cope with the trauma either because the trauma was too extensive and/or the individual's response mechanism is defective. An example of severe trauma would be massive hemorrhage and of the defective response mechanism Addison's disease. It is the surgeon's responsibility to define each type of reaction, measure those abnormalities of balance, and to correct those which demand correction. He must always stand humble, recognizing the fact that his replacement efforts are at best a poor substitute for nature's reaction to stress.

When a well-nourished, otherwise healthy individual has been subjected to a moderately traumatizing surgical procedure the immediate reactions will consist of (1) a mild fever (for which antibiotics are not indicated), probably the result of foreign protein reaction, (2) a brief period of starvation, and (3) an increased catabolism which is a result of the operation. The losses as described under *Effects of Operation* are not great and careful attention must be given to balance, avoiding the over-administration of any intravenous solution, encouraging early ambulation and early active respiratory exchange. Certain changes which have been unduly stressed by some investigators may occur. These include oliguria or anuria, an excessive excretion of potassium, retention of sodium or chloride, or excessive nitrogen excretion. In the author's experience these abnormalities may occur occasionally but represent the exceptional individual variations. When urine excretion is suppressed, except in the occasional instance, it has been shown to be transient, lasting during the day of operation and the first postoperative day. It is never harmful and it is considered advisable not to attempt to encourage urine excretion. It has been found that most complications in this type of patient are the results of over-enthusiastic mal-administra-

tion of various intravenous solutions. Administration of too much five per cent dextrose in distilled water to patients with transient urinary suppression will produce hypotonicity of body fluids with resultant convulsions, saline over-administration will produce edema, and over-administration of blood will embarrass the cardio-respiratory system. It is considered better to err on the side of under-administration because the body can cope with such situations.

Studies of the adrenal response in such patients will demonstrate first a diminished amount of circulating eosinophils and an increase in the urinary 17-ketosteroids. It is stressed that the organism can tolerate the trauma and post-traumatic period by its well integrated adaptive mechanisms. A hands-off policy is indicated for the first two to four days replacing only estimated or calculated losses. If the patient has not recuperated to the point of ambulation and oral

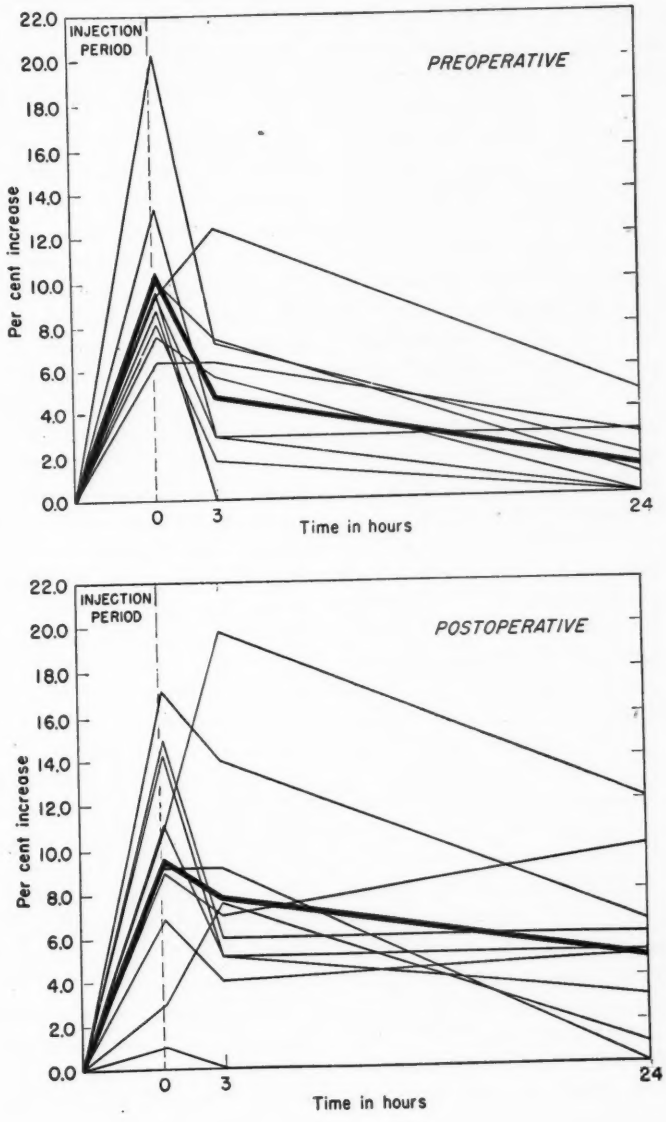

Fig. 6.

ingestion of foods by this time, a program of intervention must be charted. It is essential during this period to respect the body's ability to withstand the trauma and to watch carefully for the development of any complications. Blood volume must be maintained, careful attention must be given to hemoglobin, hematocrit, and protein levels realizing that these measurements are only measurements of concentration. Continued blood loss will become evident by diminishing hemoglobin and hematocrit; marked water loss due to unmeasured perspiration will be reflected by an increasing plasma protein concentration. It may be mentioned that in the patient receiving antibiotics the orthodox symptoms and signs of abscess formation and peritonitis will frequently be absent. The only indices of their presence will be a continued low grade fever beyond the first two postoperative days, a reluctance to ambulate, and hypoproteinemia due to loss of plasma proteins into the abscess. These complications should of course be treated by appropriate measures.

Fluids and crystalloids given to patients during the immediate postoperative period will be handled differently in many instances from that given to an unoperated person. It has been demonstrated by this author that sodium chloride solutions will be spilled in the interstitial space in greater quantity and for a longer period than the same salt load given preoperatively. It has been shown that normally proteins are mobilized into the plasma subsequent to a salt load in an effort to maintain normal osmotic relationships. In the postoperative patient this mechanism is faulty and the saline solution diffuses into the interstitial spaces. Figure 6 shows the plasma chloride concentration subsequent to a load of 27 grams of sodium chloride. The difference between the preoperative curve from that which occurred postoperatively is manifest. If hypertension or anoxia supervenes during the operation, the cell membranes become disrupted and sodium and chloride enter the cell, producing further derangements with a lowering of the plasma concentration levels of these ions.

The handling of a water load by patients postoperatively depends upon their renal excretory capacity. In a group of twenty patients given an intravenous water load of three and one-half liters during the immediate postoperative period, eight maintained good urinary excretory ability and twelve retained the administered water. In the later group, a few presented convulsions and other signs of acute water intoxication with dilution of the various plasma crystalloids. The cause for the difference of response remains enigmatic but indicates that each patient must be individualized regarding his personal reaction to a water load postoperatively.

The Complicated Response

If the surgical trauma has been extensive, if blood loss has been great and replacement inadequate or delayed, or if anoxia has occurred during the operation, the surgeon's task of conducting such patients through the immediate postoperative period will be great. Some patients who have been subjected to shocking traumatization will rebound with gratifying agility. In such instances a conservative therapeutic policy is indicated. In most such patients, however, the postoperative period is punctuated by various complications. Distressing sequelae consist of prolonged oliguria or anuria with retention of nitrogen (which produces uremia), sodium and chloride retention, and the liberation of potassium from the cells into the plasma which exerts deleterious effects especially upon the heart. The exact mechanism of this complication is not known, but it lasts usually from three to seven days after which there is a profound diuresis with urinary excretion of electrolytes. The therapy for this complication consists of a hands-off policy during the period of oliguria, supplying only such water as is lost. A mild anemia is best left untreated because some of these patients are sensitized and will develop unexplained hemolytic reactions to administered blood. The surgeon must be constantly on the alert in such instances to treat boldly by administering large quantities of electrolytes and water when diuresis ensues.

The response of the malnourished, weakened patient differs from that of the robust individual in many respects. It may vary from utter failure to institute a reaction to stress such as seen in the Addisonian patient to an effective alarm reaction but with an extreme proclivity to development of postoperative complications. In such patients a preoperative test of adrenal function as advocated by Thorn may be advisable and if the test indicates hypoadrenalism and an operation is nevertheless mandatory, the cautious administration of cortisone during the surgical period may be indicated and a postoperative regime in-

stituted similar to that utilized for patients after adrenalectomy.

In those mal-nourished individuals who had been prepared for operation by an intensive preoperative regime with the aid of surgical measures (gastrostomy, enterostomy for feeding, etc.) it has been my experience that the nutritional status of such patients is sometimes more apparent than real and after operation the "bottom drops out," with the development of hypoproteinemia, poor wound healing, increased susceptibility to infection, delay in development of peristalsis with resultant gastrointestinal distention, etc. In such patients it is advisable to push nutrients by every means possible, to avoid over-hydration and excessive electrolyte administration, to keep alert for the development of any complication, e.g., hypochloremia, and to correct it instantly before the chain reaction of metabolic disturbances develops.

It is essential to measure all losses from the body (vomiting, Wangensteen suction, diarrhea, exudates and transudates) and on the basis of their content of electrolytes and proteins to replace these, volume for volume. The surgeon can have a better index for replacement therapy by measuring the content and composition of body losses than measurements of chemical composition of the blood.

Acknowledgment

Permission has been given for publication of the following tables and figures: Table I, Ariel, Freier and Kremen,[9] courtesy of W. B. Saunders Company; Figure 2, Courtesy Dr. Jerome Gross; Table II, Figures 3 and 4, Ariel,[5] by permission of *Surgery, Gynecology and Obstetrics;* Figure 5, Ariel and Miller, reproduced from *Surgery* through courtesy of C. V. Mosby Company; and, Figure 6, Ariel and Kremen,[6] reproduced from *Annals of Surgery,* courtesy of J. B. Lippincott Company.

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Blood Transfusions and Plasma Volume Expanders

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THE ENORMOUS value of blood transfusions in anemia and in states where blood volume is depleted is well known. The indications and hazards in the use of blood are also too well known to bear repetition. The serious question may be rightfully asked, how well do we adhere to the known indications?

In an attempt to obtain an answer to this question, the transfusions given in a small general hospital in 1953 were reviewed. During this year, 284 patients received transfusions. The total number of transfusions given was 1,244. Of this group, the records of 75 patients, who received a total of 256 transfusions, were carefully reviewed.

The indications for which the blood was given are shown in Table I. It will be noted that most of the blood was given for hemorrhage. Usually this was hemorrhage occurring during surgery. Of the patients who received blood during surgery, only eight were in shock at the time. In Table II, all of the transfusions were evaluated as to whether they were indicated. It will be seen that there were nine patients who received blood for hemorrhage incident to surgery in which the reviewers thought that the blood was not indicated. Four of this group received blood during surgery. None of the patients were in shock. They had minimal blood loss, and postoperatively were found to have a polycythemia which we presume was induced by the blood transfusion. The patients given blood postoperatively had hemoglobins, at the time they received the blood, of 14.6, 14.3, 13.9, 12.9, and 11.9 grams. The two individuals who received blood for the treatment of anemia where it was considered not indicated had hemoglobins of 12.5 and 12.7 grams. One patient received blood for the chemical finding of hypoalbuminemia, although he had no symptoms related to the lowered protein content of the blood. Sixteen per cent of the total patients receiving transfusions then received blood when not indicated. In addition to this, there were another thirty patients in which blood was given at surgery where there was no shock; where the surgeon described minimal blood loss; and where it was impossible to ascertain whether or not the blood was indicated or not.

Of the total group of patients, forty-four received one or two transfusions and 31 received three or more. Thirty-eight of the patients receiving only one or two transfusions received their blood during surgery.

The reaction rate in this group of seventy-five patients was 5.3 per cent. There were two pyrogenic reactions, one allergic reaction, and one

TABLE I. INDICATION FOR TRANSFUSION.

Hemorrhage—surgery	57
No shock	49
Shock	8
Given postoperatively	9
Hemorrhage—gastrointestinal	14
No shock	12
Shock	2
Hemorrhage—traumatic	5
No shock	2
Shock	3
Hemorrhage—nasal (shock)	1
Anemia	5
Hypoalbuminemia	1

TABLE II. EVALUATION OF TRANSFUSION.

Indication	*Number Not Indicated*
Hemorrhage—surgery	
Given postoperatively	5
Given at surgery	4
Anemia	2
Hypoalbuminemia	1
Total	12 (16%)

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The studies of blood transfusions were done in collaboration with Jack Riggall, M.D., and Edward Schneider, M.D. The dextran studies in collaboration with Ben Heller, M.D., and Richard Ebert, M.D.

TABLE III. FOUR GROUPS OF PLASMA VOLUME EXPANDERS.

1. Blood derivatives
Albumin
Globin
Plasma
2. Modified Proteins
Gelatin
Oxypolygelatin
Isinglass
3. Plastics
Methyl Cellulose
PVP
4. Polymerized Carbohydrates
Acacia
Pectin
Dextran

hemolytic reaction. It is worthy of mention that the patient who had the only serious transfusion reaction, the hemolytic transfusion reaction, was one of the individuals who received blood postoperatively where it was considered that blood was not indicated. The man had a fracture of the left tibia and fibula and right femur in an automobile accident. Surgery was performed on November 19. On December 4, his hemoglobin was 11.9 grams. Despite the only moderate reduction in the hemoglobin, he was given a transfusion on December 10. After 200 cc. of blood he developed back pains, vomiting, chills, cyanosis, and tachycardia. Investigation proved that it was a hemolytic transfusion reaction. The error occurred when the pilot tubes on two bottles of blood were interchanged.

From this review, then, it is apparent that we do not always follow the indications for the transfusion of blood as closely as we should.

There are certain difficulties with the use of blood that make it advisable to have other substances available. Blood, of course, is difficult to procure and in addition to that it is difficult to store. In the event of a disaster, it would be impossible to insure an adequate supply of blood. The onset of the Korean War intensified interest in the use of other substances. These should be termed plasma volume expanders and not substitutes for blood. In Table III is a list of the various plasma volume expanders. They are divided into four main groups: blood derivatives, modified proteins, plastics, and polymerized carbohydrates. Many of these substances have received extensive clinical or experimental trial. Albumin, globin, and plasma, like blood, are difficult to procure. In addition, the incidence of hepatitis following plasma transfusion is appreciable. In the patients receiving plasma transfusions during the Korean War, the incidence of hepatitis was approximately 20 per cent. It is possible that further development of the storage of plasma at room temperature will obviate the high incidence of hepatitis following such transfusions. However, this remains to be proved and until definite proof is available, it would seem advisable to limit the use of plasma transfusions. The various blood derivatives derived from animal blood have been tried. The objective to these substances is the high incidences of reaction. Of the modified proteins, oxypolygelatin would seem to have the greatest promise. This particular substance is a modification of gelatin and does not gel at room temperature. Isinglass has been used and found to have a high incidence of reaction. Both of the plastic substances mentioned, methylcellulose and polyvinylpyrrolidine, are stored in the tissues. Methylcellulose has been found to produce renal injury. Of all of the substances listed in this table, the two that would appear to have the greatest promise are dextran, which is a polymerized carbohydrate, and oxypolygelatin. Since more information is available regarding dextran, the remainder of our discussion will be limited to the use of dextran.

Dextran is a water soluble glucose polymer related to glycogen. It is produced by the action of Leuconostoc mesenteroides on sucrose. The raw dextran has a very high molecular weight and is highly toxic for animals. By acid hydrolysis this may be degradated into material of suitable molecular weight. This material has a low incidence of reactions. It has certain other attributes which indicate that it would be worthwhile to consider as a plasma volume expander. It produces no alterations in the pulse, blood pressure, or electrocardiogram. It has no toxic effects on the kidney or liver. It does not interfere with blood typing, cross-matching, or Rh determinations. It has a low incidence of reactions. When the reactions occur, they are chiefly of an allergic type with itching, urticaria, joint pain, headaches, vasomotor collapse, and respiratory distress. The incidence of reactions has varied greatly. In Sweden, where dextran was first used, the incidence of reactions was approximately 1 per cent. In England the reaction rate was 2 per cent. At Brooke Army General Hospital utilizing the Swedish dextran, a reaction rate of 40 per cent was found.[3] More recently, with the American products, the reaction rate has been

extremely low and is probably a fraction of a per cent.

If any substance is to be used by the practicing physician, it is important that he know not only

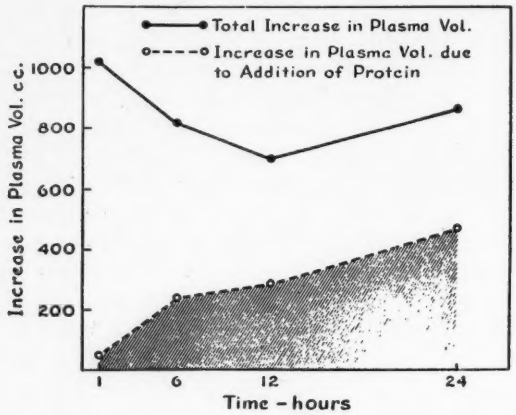

Fig. 1

what it will do, but also what happens to the material. In order to more accurately ascertain this, certain experiments were performed.[2] In the first part of the experiment, one liter of 6 per cent dextran was given to normal, healthy subjects. The plasma volume, hematocrit, protein concentration, dextran concentration, and urinary dextran excretion were determined at one, six, and twenty-four hours. In the second portion of the experiment, young, healthy, male subjects were bled one liter and then were given a liter of dextran. Similar determinations were performed.

The dextran concentration in both groups was slightly over 1 gram at 1 hour and then decreased slowly. At the end of forty-eight hours, the dextran was still detectable in appreciable quantities in the blood. In those subjects who were not bled, dextran was excreted rapidly; 23 per cent in 1 hour and a total of 48 per cent in twenty-four hours. In the subjects who were bled, similar results were obtained. Twenty-six per cent was excreted in one hour, and in twenty-four hours 60 per cent had been excreted. Of the dextran administered in those subjects who were bled, 40 grams was still circulating at the end of one hour and 25 grams at the end of six hours. A small per cent of the dextran could not be accounted for by the circulating dextran and the dextran excreted. This per cent of dextran unaccounted for gradually increased with time. This experiment supplies no information as to the fate of the dextran which could not be accounted for. However, other experiments have shown that dextran diffuses freely into the lymph and this may explain the discrepancy at 1 hour. Dextran is metabolized, which explains the loss at other time intervals. Studies utilizing dextran tagged with radioactive carbon have shown that 90 per cent was eliminated in 10 days. Of this, approximately two-thirds is excreted in the urine and one-fourth is expired as CO_2. It is assumed that dextran is metabolized to glucose and other experiments have substantiated this notion.

The administration of 1 liter of dextran produced an increase in the plasma volume of 750 cc. in one hour, which then decreased to 530 cc. in the subjects who were not bled. In those individuals who had been bled, the plasma volume after the administration of dextran was sustained as indicated in Figure 1. The shaded portion of Figure 1 indicates that portion of the increase in plasma volume which was related to the addition of native protein to the circulation. It is this addition of native protein to the circulation that accounts for the sustained plasma volume despite the excretion of dextran. It is important to determine whether the addition of native protein to the circulation proceeds at a normal rate despite the presence of dextran in the circulating blood. At the end of one hour, 3.3 grams had been added to the circulation; at the end of six hours, 15.7; and at the end of twenty-four hours, 30.6. These figures are similar to those obtained by Ebert, Stead, and Gibson[1] in experiments in which no plasma volume expander was given in subjects who were bled one liter. It then appears that dextran does not inhibit the addition of native protein to the circulation. Changes in the hematocrit and protein concentration were accounted for by the increase in plasma volume while the red cell volume remained constant. As would be expected on a percentage basis, the protein concentration decreased more than the hematocrit concentration.

The requirements for a satisfactory plasma volume expander have been outlined by the Subcommittee on Shock of the National Research Council. These requirements are: (1) maintenance of satisfactory colloid osmotic pressure; (2) constant composition, (3) suitable viscosity, (4) stability with temperature changes, (5) stability in storage, (6) ease of sterilization, (7)

freedom from pyrogens, (8) absence of immediate adverse effects, (9) absence of immediate or delayed organic derangement, (10) absence of antigenicity, and (11) reasonable price. It would appear that dextran meets all of these requirements with the exception that it may possess some antigenicity. In addition to these requirements, an additional requirement should be listed. This is that dextran or any plasma volume expander should have no effect on the addition of native protein to the circulation. Were it to inhibit this addition and still be excreted, the plasma volume would rapidly decline.

TABLE IV. FLUID PREFERRED

	Whole Blood	Cells	Dextran	Plasma	Other
Anemia	S	B	O	O	O
Acute poisoning	S	B	O	O	O
Blood dyscrasias	S	O	O	S	S
Immunotherapy	S	O	O	S	B
Hypoproteinemia	S	O	S	S	B
Shock, hemorrhagic	B	O	S	S	S
Shock, burn	S	O	S	S	S
Shock, infection	S	O	S	S	S
Cerebral edema	O	O	S	O	B

B—Best S—Satisfactory O—Not Indicated

In Table IV are listed the preferred solutions for the indication given in the left hand column. By other preparations in this table, I refer to such things as the various protein fractions. I would like to point out that dextran or any other plasma volume expander is not indicated in anemia, acute poisonings associated with reduction in the oxygen carrying capacity of the blood, blood dyscrasias, and immunotherapy. It is evident from this table that dextran may not be considered a blood substitute. Considerable experience has been accumulated with the use of dextran in the treatment of hemorrhagic shock. It is in this circumstance that it would appear to have its greatest usefulness. It has also been effective in shock associated with burns and infections, but less effective than in shock related to hemorrhage. In circumstances where there is edema related to hypoproteinemia, dextran in a salt free solution may be effective in inducing a diuresis. In cerebral edema, concentrated dextran in a salt free solution may be effective. Such a preparation is not available commercially. The commercially available dextran is a 6 per cent concentration and is in 0.9 per cent salt solution.

In summary, then, blood is the ideal solution to use when the blood volume is depleted, particularly when that depletion is secondary to hemorrhage. A review of the records of a general hospital indicated that blood had been used unnecessarily in 16 per cent of the patients. In an additional 40 per cent it was impossible to ascertain whether a clear indication existed for the use of blood. While blood is the ideal solution, in the event of a disaster it may be impossible to obtain adequate supplies of blood. Under such circumstances dextran would seem to be a satisfactory plasma volume expander. In emergencies, particularly in small hospitals that do not have large reserves of blood, dextran again may be used while waiting to obtain blood or even as the sole agent if the blood deficit is not too great. Again, I would like to emphasize that dextran is not a blood substitute. In circumstances where only small quantities of blood seem indicated, perhaps dextran could be used, but under those circumstances nothing may be better than something.

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Acute Renal Insufficiency

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IN A BASAL state in health approximately one fourth of the cardiac output, or 1,200 cc. of blood, perfuses the kidneys each minute. This amount of blood is equivalent to a renal flow of 700 cc. of plasma per minute. About 19 per cent of the plasma water that perfuses the kidney each minute is filtered by the glomeruli, resulting in a glomerular filtration rate of 130 cc. per minute.

Numerous events may precipitate an intense and persistent decrease in renal blood flow and glomerular filtration rate, and acute renal insufficiency may ensue. During the past twelve years, a syndrome of acute renal insufficiency associated with a wide variety of precipitating factors has become recognized with increasing frequency. It is of the utmost importance that the syndrome be recognized early and proper treatment instituted, as errors in diagnosis and treatment may lead to death of the patient.

Acute renal insufficiency may be defined as a syndrome of rapid, but *reversible,* loss of renal function due to renal ischemia and disseminated areas of tubular degeneration. Synonyms that have been used are acute renal failure, acute tubular necrosis, lower nephron nephrosis, shock kidney, crush syndrome, hepatorenal syndrome, toxic nephrosis, burn nephritis, acute parenchymatous degeneration and extrarenal uremia. The term "lower nephron nephrosis," which implies localization of pathologic change to the distal tubule, is a poor one despite its wide acceptance, since the renal lesion is disseminated.

Pathologic Physiology

1. Shock.—The majority of patients with acute renal insufficiency will have experienced shock. In those patients who do not manifest the clinical signs of peripheral vascular collapse, hemoconcentration and a deficient circulating blood volume frequently will be present. The studies of Lauson and associates[2] indicate that the kidney participates to a pronounced degree in the vasoconstrictive phenomena of shock. The renal ischemia is proportionately greater than the reduction in cardiac output, and the glomerular filtration rate and tubular excretory function are greatly reduced. Organic tubular damage, suppression of urine and uremia may be the sequelae. If the patient recovers, normal renal function may not be established for weeks or months.

2. Pigment Casts.—Hemolytic transfusion reactions and other disorders associated with a hemolytic process are commonly followed by acute renal insufficiency. The distal and collecting tubules are frequently obstructed by hemoglobin casts, but obstruction *per se* is often an inadequate explanation of the oliguria. The precipitation of the casts appears to be secondary to intense renal vasoconstriction and reduction of glomerular filtration rate. Flink[1] has demonstrated that the value for hemoglobin in the plasma is an important determinant in the degree of tubular damage and the development of uremia. The crush syndrome, in which large amounts of myohemoglobin are released from striated muscle, occurs through a similar mechanism.

3. Tubular Toxins.—Tubular necrosis and hydropic degeneration are caused by numerous substances. Chief among these are carbon tetrachloride, mercuric bichloride and the sulfonamides. Experimental work indicates that the reduction in renal blood flow and glomerular filtration rate is secondary to the tubular damage. Poisoning with carbon tetrachloride is a frequent cause of oliguria. The diagnosis is frequently overlooked since the patient may appear to present the problem of primary liver disease with jaundice and hepatomegaly. In the absence of liver involvement, an incorrect diagnosis of an acute exacerbation of chronic glomerulonephritis may be made. Since 1947, an average of two cases of poisoning with carbon tetrachloride have been seen at the Minneapolis Veterans Hospital each year.

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4. Mechanism of Anuria or Oliguria.—Renal vasoconstriction and reduction of glomerular filtration, together with back diffusion of that filtrate which is being formed, account for the suppression of urine. Back diffusion occurs because of damage to the tubular cells.

Clinical Course

The clinical syndrome may be divided into three phases.

1. Shock.—This has been discussed already.

2. Acute Renal Insufficiency.—There is rapid development of progressive renal insufficiency ushered in by fever, nausea and vomiting, abdominal distention, occasionally jaundice, and pain in the costovertebral angle. Diminution in urinary output to 400 cc. per day or less is the general rule, but occasionally this syndrome may develop in spite of a daily urinary output of 500 to 800 cc. per day. Anuria is uncommon. The urine may be frankly bloody or smoky for the first several days; it is acid in reaction and contains large amounts of albumin. The initial urine may have a specific gravity of 1.017 to 1.020, but concentrating ability is rapidly lost and the specific gravity becomes fixed at 1.008 to 1.012. The urinary sediment contains erythrocytes, leukocytes, pigment casts, and hyaline and granular casts. A rapidly progressive normocytic normochromic anemia develops that may continue for several months.

As the oliguria persists there is a great tendency for the development of signs of congestive heart failure with pulmonary edema. This is especially true if salt and water are administered injudiciously. Hypertension may develop after the first few days, the systolic hypertension being more pronounced than the diastolic. Hypertension is not invariable. Six of twenty unselected patients seen at the Minneapolis Veterans Hospital did not have hypertension.

Gastrointestinal symptoms may continue in this phase, with abdominal distention, nausea and vomiting, and diarrhea. These symptoms, as is true of all others, may vary greatly from patient to patient.

Cerebral symptoms are common. There may be restlessness, delirium, stupor, and coma. Convulsions occur but are not common.

Early deaths are usually due to the primary disease, but fatal pulmonary edema may occur early if incorrect therapy is given. Deaths after the tenth day are due to pulmonary edema, uremia, or hyperpotassemia.

Laboratory tests reveal: a rapid fall in hemoglobin to 8 to 10 grams per 100 cc. of blood, with stabilization at this level; a rapidly rising blood urea nitrogen, decreased serum sodium, chloride and bicarbonate; and varying elevations of serum inorganic phosphorus and potassium. Potassium commonly rises to levels that are neurotoxic and cardiotoxic, especially if the serum sodium is low. Muscular weakness and pain, respiratory paralysis and flaccid paralysis of the extremities may occur when the serum potassium is at levels above 7.5 to 8 mEq. per liter. The first electrocardiographic abnormality is the presence of high peaked T waves, with a narrow base, noted initially in the precordial leads (usually V_2 first) and then in the limb leads. This may quickly be followed by depression of the ST segment, varying degrees of auriculoventricular and intraventricular block, disappearance of the P wave, and ventricular fibrillation. The sequence of events may be so rapid as to catch the unsuspecting physician off guard.

3. Recovery Period.—As tubular regeneration occurs, there is a gradual increase in urinary volume and diuresis occurs. The data of Swann and Merrill[3] indicate that diuresis is related to retention of water during the oliguric phase, this water probably coming from the oxidation of fats. There are some patients in whom depletion of the volume of extracellular fluid and circulating blood will be followed by circulatory collapse, but this is not the general rule. The blood urea may continue to rise for several days after diuresis occurs. This is usually not cause for alarm and steady improvement in the clinical course will be noted. In some instances, however, symptoms and signs of acute renal insufficiency will progress in spite of diuresis. After clinical recovery, normal renal function may not be reestablished for many months.

Differential Diagnosis

The following diseases must be considered in differential diagnosis: acute glomerulonephritis, acute exacerbation of chronic glomerulonephritis, acute or chronic pyelonephritis, ureteral obstruction from calculus, sulfonamide crystalluria, meta-

static cancer and renal vascular lesions, such as malignant hypertension and renal infarction. As a general rule, in the absence of a history of an event known to precipitate acute renal insufficiency, the diagnosis will usually prove to be another form of renal disease.

Treatment

Principles.—There are several important principles governing therapy:

1. Renal ischemia produces a *reversible* renal shutdown. Tubular necrosis is potentially reversible, and the renal lesion may heal completely.
2. The kidneys cannot be "flushed out" by large amounts of salt and water in the presence of oliguria or anuria.
3. The principal cause of death is pulmonary edema.
4. Hyperpotassemia results from intake of potassium as well as from breakdown of tissue.
5. In a 70-kg. man with sudden cessation of renal function, loss of 1,000 cc. of insensible water occurs daily. The preformed water of oxidation is about 470 cc. daily, leaving a daily deficit of 530 cc.
6. Administration of carbohydrate will spare breakdown of protein.
7. The phase of diuresis cannot be accepted as one of complete recovery, and the patient must be carefully observed in this phase.

Measures.—Therapeutic measures in keeping with the principles just noted may be outlined as follows:

1. Combat shock promptly with effective measures.
2. Evaluate urinary output in any patient in whom the diagnosis is suspected before ordering parenteral fluids.
3. No more than 500 to 750 cc. of a 10 to 15 per cent solution of glucose should be given daily. In the usual case 500 cc. daily will suffice.
4. If the patient is able to tolerate fluids orally, either emulsions of fat (Ediol) or a modified Borst regimen of butter soup and butter balls may furnish sufficient calories in a small amount of fluid to decrease cellular breakdown with its attendant biochemical abnormalities.
5. Keep in mind the susceptibility to pulmonary edema. Whole blood is *not* indicated to correct the developing anemia. Avoid use of sodium chloride even in small amounts. Do not give sodium bicarbonate unless metabolic acidosis threatens life.
6. Frequent serial electrocardiograms and measurements of serum potassium, when available, are necessary to evaluate hyperpotassemia.
7. Insulin and glucose (1 unit for each 3 to 5 grams of glucose), may be used as an emergency measure to combat hyperpotassemia. In critically ill patients such treatment may be followed by hypoglycemia.
8. If the patient is being treated properly during the phase of acute renal insufficiency, he will lose about one-half pound per day. If body weight is maintained or is increasing, overhydration is present.
9. In the early recovery phase parenteral fluids must be given with caution since there is a delayed diuretic response to water. Pulmonary edema and cerebral symptoms may recur with injudicious use of salt and water. After twenty-four to forty-eight hours of the early diuretic phase, daily loss of salt and water may be safely replaced over a period of twenty-four hours. Urinary volumes and the concentrations of electrolytes in urine and serum may serve as guides to replacement therapy.
10. With the onset of recovery, a moderate-protein, high-carbohydrate diet is indicated.
11. As noted by Swann and Merrill,[3] any sensible plan for restricting water, sodium, chloride, potassium and protein and providing calories as carbohydrate will result in low morbidity rates and recovery. In some severely-ill patients, especially those with hyperpotassemia, the artificial kidney may be lifesaving.

Prognosis

Patients with acute renal insufficiency secondary to chemical toxins appear to have a milder course and to regain normal renal function more rapidly than do those whose condition is secondary to traumatic, oligemic or postoperative shock. This may be correlated with the degree of negative nitrogen balance and cellular breakdown, which is more intense in the latter group. The mortality rate has been extremely high (80 to 90 per cent) in the past. With a sounder understanding of the reversibility of the renal lesion and the pathologic physiology, better treatment has sharply decreased this mortality rate.

(References on Page 59)

Alterations of Carbohydrate Metabolism Following Trauma

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IT HAS been known for years that injury may produce abnormalities in carbohydrate metabolism. As early as 1854, Goolden[30] reported that patients who sustained an injury not infrequently had considerable sugar in the urine, accompanied by a diuresis. As the patient's condition improved the glycosuria disappeared, in many instances within ten days. Following these observations, Claude Bernard and others referred to transitory hyperglycemia and glycosuria following various types of trauma. In 1911, Cannon, Shohl and Wright[14] showed that an emotional glycosuria could be produced in animals but it did not occur after an adrenalectomy with a comparable stress. In 1914, Epstein and Baehr[27] reported an elevation in the blood sugar concentration following hemorrhage, and two years later Epstein and Aschner[26] concluded that anesthesia also played an important role in the production of hyperglycemia. Several years later, Keeton and Ross[33] found about a 100 per cent increase in the blood sugar concentration in normal dogs after they had been under ether anesthesia for two hours. Cannon[11] and Aub and Wu[8] demonstrated hyperglycemia following traumatic shock, and Underhill and co-workers[46] described the same finding in patients following a thermal burn.

In 1925, Davidson and Allen[21] reported studies on numerous patients following head trauma. Figure one is a composite summary prepared from their data. They noted that blood sugar concentrations, after the intravenous administration of 125 ml. of 25 per cent dextrose, were higher in patients following a concussion of the brain than in the same patients later during convalescence or in normal control subjects. Twenty-four to thirty-six hours after a skull fracture the blood sugar values were even higher and "the fall of the curve to the fasting level was still more delayed." They concluded that concussions of the brain and fractures of the skull produced

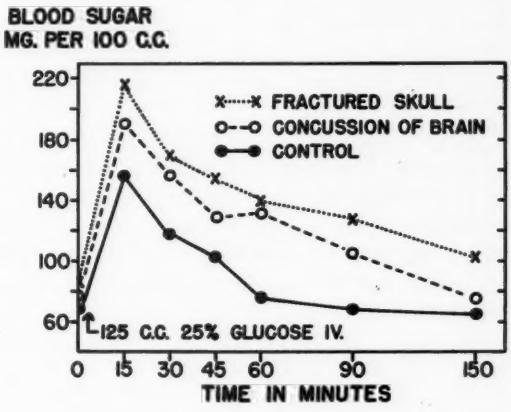

Fig. 1.

a profound, though temporary, derangement of carbohydrate metabolism and that the more serious the injury, the more striking was the disturbance in the blood sugar levels following the administration of glucose.

It was studies such as these and the results of the nitrogen and chloride balance data reported by Davidson and his associates[20,21] on burned patients, and the reports of other investigators[12,19,44] over the next few years, that eventually led to our present-day concept of the pituitary-adrenal relationship to the findings noted after injury.

In 1938, Thomsen[45] reported his results of extensive studies on traumatic diabetes. He concluded that post-traumatic disturbances in the carbohydrate metabolism, manifesting themselves by spontaneous or alimentary glycosuria and hyperglycemia, were evident in a considerable number of previously normal persons. He also noted that the kind and location of trauma was not of prime importance since there was no difference

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between head trauma and peripheral injuries. He concluded that "a physical trauma may give rise to an exacerbation of existing diabetes, but the exacerbation manifesting itself immediately after the trauma is only temporary."

During the past twenty years, more information concerning the role of the pituitary and adrenal glands has been published. In 1940, Long, Katzin and Fry[36] noted that adrenalectomized rats, who refused food and sodium salts, or were forced to fast, show a marked depletion of liver and muscle glycogen. These workers noted that such changes could be prevented by the administration of adrenal cortical extract and that under this therapy liver glycogen could be increased well above normal, even in fasted animals, thus confirming previous observations of Britton and Silvette.[10]

When the adrenocorticotropic hormone and cortisone became available, numerous other significant contributions to our understanding of the metabolic alterations noted following trauma or stress appeared. In 1948 and 1949, Conn and his associates[17,18] reported the results of their metabolic balance studies of three normal young adults who were given ACTH intramuscularly for eight to ten days, following a control period. These subjects demonstrated hyperglycemia and glycosuria, as well as a plateau type glucose tolerance curve. Two of the subjects exhibited a negative nitrogen balance and lost large amounts of body protein, despite an adequate oral food intake.

We have been concerned with the metabolic alterations following burns and lesser forms of *trauma* for a period of twelve years and are particularly interested in the possible therapeutic measures which might be employed to reduce the morbidity and mortality of the post-traumatic patient. More recently, we have been interested in carbohydrate metabolism, since with the advent of fructose and invert sugar new materials are available which are metabolized differently than glucose.

Time does not permit a review of numerous contributions[1,9,15,16,22,28,50] which led ultimately to the clinical use of fructose and invert sugar during the past few years.[23,24,38,41,47,48,49] Because recent studies[38,41] indicated that the metabolism of fructose differed from that of glucose in both the normal and diabetic subject, and because the metabolism of fructose in the person with diabetes, even in the absence of insulin, is similar to that seen in a normal subject, it was decided to undertake studies in postoperative patients to determine whether the two sugars would be utilized differently. The results of these studies have been presented previously.[23,24]

Price, Cori and Colowick[42] proposed that insulin acts on the hexokinase, which converts glucose to glucose-6-phosphate, whereas the phosphorylation of fructose is under the control of a different hexokinase which is not affected by the lack of insulin. It therefore seemed important to determine if the hyperglycemia and glycosuria seen postoperatively was due to an impairment of the glucokinase activity. If such were the case, the metabolism of fructose in such patients should be normal. Accordingly, fructose and glucose in amounts of 1.0 gm. per kilogram was administered intravenously as a 10 per cent solution over a period of sixty minutes to patients on alternate days preoperatively and postoperatively. Five otherwise normal adult males, undergoing a unilateral herniorrhaphy, under spinal anesthesia, were used for this study, and blood samples drawn periodically were analyzed for glucose, fructose, pyruvic acid and serum inorganic phosphorus. The results indicated that while a higher glucose tolerance curve was obtained postoperatively than preoperatively, the postoperative fructose tolerance test was essentially the same as that noted preoperatively. The blood pyruvic acid levels and serum inorganic phosphorus concentrations indicated a better utilization of glucose preoperatively than postoperatively and also that the metabolism of fructose was essentially unaltered by operation. The four-hour excretion of hexose in the urine during and immediately after the tolerance tests indicated that more glucose was spilled postoperatively than preoperatively and that more hexose was present in the urine following the administration of glucose preoperatively than occurred postoperatively after fructose.

In subsequent studies,[4] glucose tolerance curves were obtained in patients undergoing a more severe type of stress or operative trauma. In such patients, the glucose level in the blood, observed after the intravenous glucose tolerance test, was higher than that noted following a herniorrhaphy, and the abnormality persisted for a longer period of time. In patients undergoing a gastrectomy, even though the glucose was infused at a slightly slower rate, it was not unusual to find 5 to 45

gm. of sugar (equaling from 2 to 30 per cent of that infused) in the urine per twenty-four hours during the first five to six postoperative days.

Other workers have made similar observations and noted that fructose and invert sugar could be better utilized than glucose.[47,48,49] Several groups [0,25,40] have also presented evidence to show that the utilization of nitrogen might be enhanced by the simultaneous administration of a hexose (especially fructose). While more work along this line must be done before definite conclusions can be reached, these observations may be of importance in helping to minimize the wasting of the body tissues following a severe injury.

Albright[7] has reported, in detail, the metabolic alterations that occur in patients with Cushing's syndrome. He presented glucose tolerance curves in four such patients. They all showed a very high fasting blood sugar level and a typical diabetic type of curve. Recently, glucose and fructose tolerance tests were done in a patient with Cushing's syndrome preoperatively while she was a diabetic and again several months after a total adrenalectomy.[3] The diabetes which had been present for several years was completely alleviated by the adrenalectomy. A typical diabetic glucose tolerance curve was obtained preoperatively, and a normal curve was present several months postoperatively. The preoperative and postoperative fructose tolerance curves were similar, indicating no interference with this hexose in hyperadrenocortical states. Since such patients presumably exhibit these changes because of an excess of the sugar or S hormone it is conceivable that a comparable derangement of endocrine activity exists temporarily following trauma.

The problem of therapy is still somewhat confused, but because of the information which has accumulated during the past ten years, some specific recommendations can be made. We feel that it is not desirable to force-feed, either orally or parenterally, the very ill or severely injured patient for the first few hospital days. These conclusions were reached after attempting early forced feeding in patients following a severe thermal burn.[2,31] Detrimental effects were noted by forcing a high caloric, high protein diet during the period of acute illness. However, after several days in the more severely injured patient and in patients exhibiting lesser forms of trauma, such as that induced by most surgical operative procedures, an adequate well rounded diet containing all necessary nutrients should be given.

If this cannot be accomplished orally, or if the giving of food by mouth is undesirable, intravenous alimentation should be used. Our studies[4,5,35] done during the past two years indicate that considerable loss of body weight and negative nitrogen balance might be prevented, at least in part, by the giving of 1,600 to 3,200 calories and 12 to 15 grams of nitrogen. While an insufficient number of patients have been studied, we have noted a better maintenance of weight, and a smaller loss of nitrogen if an intravenous fat emulsion and 250 to 350 grams of sugar are given in conjunction with an adequate protein intake. We noted that patients with peritonitis who have received amino acid solutions intravenously, along with other nutrients, showed considerably less nitrogen deficit than others who were maintained solely on intravenously administered carbohydrate. These impressions are in keeping with the results reported by Madden and Clay[37] who did nitrogen balance studies before and after the production of a turpentine abscess in dogs. They found that an increased catabolism of protein was responsible for an accelerated loss of nitrogen in the urine and were able to reduce the nitrogen deficit by supplying large amounts of protein.

Our studies[5] also tend to confirm the experimental work of others[32,39] that marked abnormalities in electrolyte balance *per se* will induce a negative nitrogen balance or a catabolic response. Non-operated patients with pyloric obstruction exhibited glycosuria and increased nitrogen loss which could be nearly or even entirely negated by the administration of the proper electrolytes, without need of additional calories or protein. Although recently[13,29,34,43] there has been considerable emphasis on the role of potassium and its possible relationship to carbohydrate and protein metabolism, in our patients we have been impressed with the alteration noted following a sodium deficiency. We do not wish to minimize the importance of potassium, but since more rapid and extensive deficits of sodium frequently occur, the importance of this ion should not be overlooked. This is especially true since we are passing through an era of sodium restriction. In many instances, in our opinion, this is well beyond that which is good for the patient. The importance of sodium was recently re-emphasized during studies[5] on patients with pyloric obstruction who were losing

considerable quantities of fixed base (especially sodium). During a seven day period one of these patients, who received moderately large amounts of sodium and potassium, developed cumulative deficits of over 500 mEq. of sodium and a 108 mEq. of potassium. In spite of an adequate intravenous caloric and protein intake, he showed a negative nitrogen balance and glycosuria. In previous studies[4] we were unable to demonstrate any effect on protein and carbohydrate metabolism when deficits of 100-400 mEq. of potassium existed. In spite of deficits of this magnitude (which represented only a 3-12 per cent decrease of the total body potassium) our patients showed a normal glucose tolerance curve and no significant effect on protein metabolism. The administration of 100 to 150 mEq. of potassium daily for several days, after permitting deficits of the aforementioned magnitude to accumulate, again showed no demonstrable effect.

It now is well established that the first aim in parenteral therapy is a restoration of blood volume and the correction of an abnormal electrolyte pattern (extracellular or intracellular compartmental deficits or excesses and acid-base balance). The prompt institution of such therapy constitutes an emergency and should take precedence over all other types of nutritional supplementation. At the same time, however, after specific immediate therapy is begun, there is no need to neglect the nutritional aspects of convalescence when there are now available parenteral solutions which contain adequate amounts of nitrogen, fat and carbohydrates, and by employing combinations of these to which the necessary minerals and vitamins have been added, one can provide complete and adequate nutrition. The many and varied facets which characterize man's response to stress must be considered as a whole and the therapy planned to adequately correct or protect as many of these features as possible. In this manner one can approach an ideal type of treatment which will minimize the effects of the stress, improve the convalescence, and diminish the mortality rate.

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Discussion

DR. JACOBSON: It has been previously pointed out that there is an apparent difference between the hyperglycemia following use of adrenal corticotropic hormone and that of true diabetes. Dr. Conn has shown that glutathione is increased in the blood in cases of ACTH-induced hyperglycemia, whereas this substance is not elevated in true diabetes. Other authors have differentiated so-called "steroid diabetes" and "pancreatic diabetes." At least one other difference between these two types of diabetes is the degree of insulin sensitivity. It has been shown that patients with "steroid diabetes" are relatively insensitive to insulin. I would like then to ask Dr. Abbott to discuss observations to which he has made with regard to the degree of sensitivity to insulin in postoperative hyperglycemia. I would also ask him to describe the role of insulin in the treatment of this type of hyperglycemia.

DR. ABBOTT: In regard to the question concerning insulin, we have not had a great deal of experience with its use in non-diabetic postoperative patients.

The glucosuria and hyperglycemia that we have seen after major operations have not been, on the whole, severe enough or persistent enough to warrant use of insulin. A few studies have been started in an endeavor to determine the answer to some of the problems that Dr. Conn and others have pointed out. Dr. Rice says that he has used insulin in the treatment of patients exhibiting postoperative hyperglycemia. I have been satisfied that utilization of some of the other sugars (invert or fructose), with slow administration, will prevent severe hyperglycemia and the glycosuria will be relatively mild.

Dr. Beal recently gave 400 to 500 grams of sugar per day in the form of 20 to 25 per cent solutions of dextrose. It was administered at the rate of about 1 gram or less per kilogram of body weight per hour. In those patients he observed less than a 10 per cent spillage of sugar.

I enjoyed the paper Dr. Heller presented dealing with anuria. We have been interested in this problem for the past ten years and I think that with the artificial kidney which we have used (Skeggs-Leonard kidney) we have been able to extract as much as 1,200 cc. of water per hour, so that over a period of five or six hours it is not difficult to remove six or seven liters of fluid. We have noticed that patients with pulmonary edema and overhydration show great improvement when water has been extracted. These patients have been then returned to a normal state of hydration, and have shown a more dramatic clinical improvement than almost any of the other types of patient.

At Walter Reed Hospital, I recently had occasion to observe a patient who was severely traumatized. Within two days he showed extremely high values for serum potassium and blood urea nitrogen so that he had to be dialyzed three times in a period of about nine days in order to alleviate the effects of hyperakalemia. Most of the potassium was coming from a crushed necrotic muscle of his lower extremity. The condition was greatly relieved when an amputation was performed. The patients we see clinically, such as those with chronic renal disease or acute renal shutdown following a transfusion reaction, or after poisoning with bichloride of murcury of sulfonamides, are much easier to care for than those we encountered during the war in Korea, because of the lack of trauma. The existence of an associated injury and the catabolic phase that follows greatly accelerates the danger and rapidity of hyperkalemia.

QUESTION: Dr. Elman, do you hesitate to give amino acids in the presence of liver damage?

DR. ELMAN: Originally I did, because I have observed a number of patients suffering from severe liver disease in whom the level of blood amino acids was high. Thus I reasoned that amino acids were not being utilized. Subsequently, Dr. Stewart of Buffalo gave amino acids to a number of patients with jaundice and other evidences of severe liver disease; as far as he could tell clinically and chemically, amino acids were utilized just as well as in the normal individual. Later, the Thorndike laboratory in Boston obtained evidence to show that intravenous administration of amino acids, along with albumin, was beneficial in severe liver disease. We have seen a number of patients suffering from hepatic coma. I had one patient who was extremely grateful when she came out of hepatic coma by responding beautifully to the intravenous feeding of glucose and amino acid as well as pure albumin. All the work done on liver disease and liver regeneration indicates the nutritional value of protein as well as carbohydrate in the resistance to hepatotoxins and the ability to overcome liver damage.

The old experience with chloroform poisoning proved that the administration of carbohydrate to patients with damaged livers enabled them to withstand the effects of such poisoning. In fact, that was the way patients were prepared for operation when chloroform was to be used. When protein as well as carbohydrate is added, the beneficial effect on the liver is increased. As a result of all these observations, I have changed from my original opinion and now I feel that protein is an extremely important part of nutritional therapy in patients with severe liver disease.

I would like to emphasize again that parenteral nutrition in any form to be used only when patients cannot obtain nutrition by mouth.

QUESTION: Dr. Elman, will you compare the relative values of blood and amino acids in correcting protein deficiency?

DR. ELMAN: I think we are dealing with two entirely different types of deficiency. One group of proteins comprises the circulating proteins, namely hemoglobin and plasma proteins. The other consists of the fixed proteins, or tissue proteins.

If there is a deficit in circulating proteins, which may occur even though the concentration is normal, the simplest, most direct and quickest way to correct that defi-

ciency is to give enough blood to eliminate the deficit. The tissue or fixed proteins, normally are not replaced by that method. The physiologic way in which a deficiency of tissue protein can be restored is to enable those tissues to make their own protein by presenting them with the proper mixture of amino acids and polypeptides.

This can be done by letting the patient make his own amino acids from the protein that he ingests and digests normally, or amino acids can be administered parenterally. Tissues can also utilize intravenously injected whole blood (hemoglobin and plasma protein) by a roundabout way that is to a certain extent unphysiologic because it does not happen normally. If enough blood or plasma is given for this purpose, and some workers have advocated this as a method of feeding protein, the excess leaves the blood stream. The tissue proteases break down this protein and hemoglobin and the resulting amino acids are picked up and fabricated into tissue protein. This may begin rather soon after the injection has been given, but it is rather prolonged process: it takes about ten days for completion, according to studies of Fuller Albright and his co-workers.

I feel that since it is really unphysiologic and delayed, and since, in most cases by the end of ten days the patient should be able to take food by mouth, this method of furnishing the tissues with amino acids should not be used. Furthermore, it is more expensive than giving amino acids directly into the vein.

I prefer to give patients blood to restore the deficiency of the circulating proteins. As soon as patients can tolerate food by mouth, I prefer that they receive as soon as possible large amounts orally; usually 200 to 300 grams of protein per day, with 4,000 to 5,000 calories given if a severe deficiency is to be corrected rapidly.

QUESTION: Dr. Lowe, would you like to discuss anything further regarding the problem of amino acid therapy?

DR. LOWE: We feed infants with a mixture of amino acids, protein and carbohydrates. When amino acids are given by mouth, allergic reactions are minimized and digestion is spared; in other words, the body gets an already completely digested protein and does not have to break it down by means of the proteolytic ferments of the stomach and the intestine. The amino acids are available immediately and these can be absorbed directly and rapidly. I imagine there must be certain conditions in which the gastrointestinal tract is only partly disabled and can handle some food, though it may need a little help by being given predigested or completely digested proteins.

We have provided additional calories by substituting alcohol. These children seem to grow adequately on it. We have used the type of mixture which Dr. Rice has given intravenously. I don't think that anybody has been quite successful in keeping a complete nutritional balance by the intravenous use of alcohol. We did this just to see if it would make babies grow. We used the mixture which Dr. Rice has used for his complete parenteral feeding. We found some difficulty in using it because it irritated the veins.

DR. ELMAN: I, too, would like to comment on that subject. We have given alcohol intravenously and I don't really know why I don't use it more frequently. The only objection I have found is that the patient's room smells of the alcohol which is excreted in the expired air. That is obviously just a prejudice. I don't know why social taboos should interfere with the progress of science, but apparently in this case they do.

QUESTION: In acute renal insufficiency there is frequently a profound hypochloremia. This does not necessarily mean sodium loss, but is usually a reflection of a shift in electrolytes. A common error in treatment of acute renal insufficiency is to attempt correction of hypochloremia by administration of salt solution. It is now clearly understood that hypochloremia itself is not an indication for the administration of saline solutions. I would like to ask Dr. Heller whether saline solution should ever be a part of the replacement program for patients with acute renal insufficiency. Specifically, should saline be used for replacement of fluid lost by emesis?

DR. HELLER: Sodium chloride should not be replaced during the phases of renal insufficiency or the phase of oliguria, even if the patient is losing small amounts of sodium chloride by vomiting. These patients have a tremendous susceptibility to pulmonary edema. Freeberg, in reviewing the literature, has shown the importance of differentiating between what I call primary heart failure and heart failure that is secondary to renal insufficiency wherein too large amounts of salt and water have been replaced during the oliguric phase. These patients who have decreased sodium and chloride in the serum do not seem to be affected by this decrease, but they can die as the result of small amounts of pulmonary edema. As a matter of fact, a shift of 300 to 500 cc. of fluid into the lungs can be fatal. I think it would be much safer not to replace any salt lost during the phase of oliguria and much safer to give no sodium bicarbonate or sodium lactate unless one feels that the state of acidosis is actually threatening the life of the patient.

QUESTION: It is my impression that while there are complex factors which control the excretion of potassium, the single most important factor is the urinary volume. Even in the face of severe renal damage, hyperpotassemia is unlikely when the urinary volume is more than 500 cc. per day. I would like to ask Dr. Heller to discuss further the factors which are important in the development of hyperpotassemia in acute renal insufficiency.

DR. HELLER: In most instances the hyperpotassemia is related to urinary volume. When patients manifest cardiotoxic and neurotoxic symptoms and signs of hyperpotassemia, the urinary volume is usually less than 400 cc. per day. This, however, is not universally true. Some patients may excrete as much as 800 cc. of urine per day and still have fatal hyperpotassemia. Lethal hyperpotassemia may occur even during the phase of diuresis. Dr. Flink and I have had the opportunity of

seeing patients at Veterans Hospital in Minneapolis who developed severe hyperpotassemia after the phase of diuresis had begun and when the patient was excreting more than a liter of urine per day. It has also been noted that in patients with traumatic or oligemic shock—because of the markedly negative nitrogen balance—hyperpotassemia may be a more serious problem than it is in the acute renal insufficiency that occurs after poisoning with carbon tetrachloride.

QUESTION: Recently forced high-fat, low-protein oral feeding has been recommended in acute renal insufficiency. I would like to have Dr. Heller discuss the use of such a forced feeding program.

DR. HELLER: Oral treatment for patients with acute renal insufficiency unfortunately is unsatisfactory because of nausea, vomiting and diarrhea. Many of these patients have abdominal distention. Such patients cannot take any food or fluid by mouth. For those who can take small amounts of oral feedings, the use of *Ediol,* which is a high-caloric-fat-emulsion mixture, or the use of the forced regimen as modified by Dr. Flink's wife through the use of butter soup and butter balls, can be highly successful in patients who can tolerate such a mixture. One of the most ideal patients that I have ever treated received what I now call "Mrs. Flink's butter-ball soup mixture." This is a mixture of cornstarch, glucose and butter that really is quite palatable. This patient had carbon tetrachloride poisoning and was able to tolerate butter soup feedings by mouth. His blood urea nitrogen never rose above 165 mg.; the phosphate did not rise to the extremely high levels so often seen; the potassium did not get above 6 mEq. per liter and the carbon dioxide combining power did not fall below 17 mEq. He made one of the smoothest recoveries I have ever seen. I feel that in a small number of such patients with acute renal insufficiency who can tolerate oral feedings, the sparing of protein breakdown can definitely facilitate recovery.

QUESTION: Dr. Heller, will you please discuss the relationship of preoperative electrolyte imbalance and the age of the patient, as they pertain to the frequency of postoperative acute renal insufficiency?

DR. HELLER: The spectrum of acute renal insufficiency is broad. Renal function may be impaired during and after operations. It is not known how small degrees of impaired renal function, as may be seen during the first twenty-four to forty-eight hours after operation, fit into this syndrome. The role of metabolic alkalosis in this syndrome is likewise unknown. A renal biopsy done on Dr. Hay's service at the Minnesota's Veterans Hospital, on a patient who had metabolic alkalosis from pyloric obstruction appeared to be entirely normal.

If a patient manifests a greatly impaired balance of electrolytes and water preoperatively, we feel that this situation should be corrected. The urinary volume should then be carefully observed in six hours to make sure that acute renal insufficiency is not developing. As already mentioned, the administration of too much fluid to a patient who has oliguria can be fatal because of pulmonary edema.

QUESTION: Dr. Ariel, do you wish to comment on the problem of acute renal insufficiency?

DR. ARIEL: It is extremely difficult to differentiate carefully between acute renal insufficiency and renal insufficiency due to metabolic alkalosis. We see an average of one patient every two weeks, who, after surgery, is suffering from loss of water or electrolytes. Undue loss from an ileac stoma, undue drainage because of Wangensteen suction or failure of proper administration of certain fluids may be the cause. Most of these patients have a high blood urea nitrogen. In addition, we see oliguria and a decrease in chloride. The carbon dioxide combining power is usually elevated and the sodium and potassium values vary from normal to abnormal. These patients are sick; they will not eat because they are nauseated, and they vomit. They must have fluid and electrolytes. Administration of a polyionic solution of electrolytes will relieve them overnight. This solution must be given boldly and with complete appreciation of the defect. As soon as the solution is given, urinary output increases. Blood urea nitrogen comes down within twenty-four hours and the electrolyte status becomes normal. If unattended, I don't know whether or not such patients would go into a state of renal insufficiency. Thus it becomes paramount to differentiate the acute anuric syndrome due to renal damage from that due to metabolic alkalosis. In one case fluid is withheld, as Dr. Heller has said, and in the other, fluid and electrolytes are forced to keep the patient out of danger.

QUESTION: Dr. Hammarsten, will you discuss further your explanation of a patient with acute gastrointestinal hemorrhage and a hemoglobin of 12 grams in whom hemodilution has not occurred?

DR. HAMMARSTEN.—My awkward six-year-old boy went out to feed the hogs on my farm. The hog feed is mixed with water in a ratio of one to four. After mixing the hog feed, he tripped and spilled some of the mixture. The concentration of feed to water was then determined and found to be the same as it had been previously. He didn't have time to return and add more of the feed, so he restored the mixture to its original volume with water. Then the concentration of hog feed became lower. In this illustration the feed, of course, represents red blood cells and the water represents blood plasma.

QUESTION: Dr. Hammarsten, do you recommend weighing the blood lost at operation and do you recommend full replacement of such calculated blood loss?

DR. HAMMARSTEN: As an internist, I have criticized the surgeon and anesthesiologist for giving blood when it isn't indicated. Accurate measurement of the amount of blood lost would be of more value than a guess. When only a few hundred cubic centimeters of blood are lost, I do not see that it would necessarily need to be replaced. On the medical service we sometimes withdraw that much blood in doing laboratory procedures.

DR. ELMAN: I would like to comment on that problem. I agree wholeheartedly with everything that Dr. Hammarsten has said about the excessive use of blood

and other parenteral fluids. However, in massive upper gastrointestinal hemorrhage we previously gave just enough blood to get the patient out of shock, but more recently we found that that policy often led to disaster.

When confronted with massive hemorrhage we aim to give as much as is needed to replace the blood lost. We do not try to restore the hemoglobin to 14 or 15 grams, but rather to a minimum of 10 grams. We would operate if there were evidence of persistent or recurrent bleeding. In about 50 per cent of these cases, the massive hemorrhage stops spontaneously, and then we can operate electively as indicated; in the other half, operations are done as emergencies.

QUESTION: Dr. Ariel, would you like to make some remarks about this problem?

DR. ARIEL: We have given Dextran solutions in place of blood to patients on the operating table. These patients have tolerated the procedure well. Our biggest difficulty, however, has been in estimating the blood volume of the patient the next morning because the Dextran has so diluted the blood that determination of the hemoglobin and hemocrit has lost its value, and it is impractical to determine blood volume routinely.

QUESTION: Dr. Ariel, would you have any ideas about proper estimation of blood volume after operation?

DR. ARIEL: The methods employed today for measurement of blood volume are not accurate enough to provide a good estimate of what the patient's expected normal blood volume should be. If the blood volume is calculated from the height or weight or surface area of the individual, there will be a 10 or 15 per cent error. Studies by Dr. Lyons, and more recently by Dr. Ellison in Columbus, show that many of the cancer patients whom we transfuse come to the hospital greatly depleted. Many of them are malnourished and have blood volumes that are extremely diminished even though the concentrations of plasma protein and hemoglobin and the hematocrit value may be relatively normal. These patients have been anemic for long periods and have compensated for it; yet they are sitting on a keg of dynamite, because they cannot tolerate the shock after a relatively small loss of blood. On the other hand, we should not pour blood indiscriminately into healthy individuals who have no need for it. I believe with Dr. Elman that the loss of a few hundred cubic centimeters is hardly enough to require replacement.

QUESTION: Dr. Seldin, would you discuss the management of a dynamic ileus in a patient with congestive heart failure, who requires continuous nasal gastric suction? Also please discuss the problem of hypochloremia in such states.

DR. SELDIN: It is well known that potassium deficiency may eventuate in *ileus*. To that extent that gastrointestinal suction produces a deficiency in potassium, it is sensible to administer potassium when ileus exists in order to replace the deficit. This may be sufficient to overcome the ileus and the condition may be reversed.

In congestive heart failure, there is massive expansion of extracellular fluid so that gastric suction may eventuate in no overall salt depletion in the sense that the patient may still be edematous even though large amounts of salt, chloride and acid have been removed from the gastrointestinal tract. The administration of potassium may be sufficient to correct the potassium deficit as well as the alkalosis. At times the administration of small amounts of ammonium chloride may help.

This panel has been so blissful and so full of accord on every event, that I hesitate to interject a note of dissent, but I would like to register a gentle protest against the position that almost everyone seems to have agreed upon. Dr. Heller has vigorously and distinctly formulated the idea that salt should not be used in acute tubular necrosis. The impression that one gleans from this discussion is that if one waves five grains of salt beneath someone's nose, pulmonary edema will ensue, with a lethal outcome. I would like to make a few preliminary remarks on this score because I don't think they are irrelevant.

A large proportion of lower nephron nephrosis is a simple consequence of salt-depletion shock. This could have been predicted from the work of Darrow long before potassium became the magic cause of all human ailments. Salt-depletion shock is a well-known entity. The net result of salt depletion is a catastrophic fall in renal plasma flow and the glomerula filtration rate, oliguria and even anuria. In its early stages, salt-depletion shock is completely reversible by the administration of adequate amounts of salt and water. The term "acute anuria" or "acute renal insufficiency" includes at least two distinct stages. In one there has been an anatomic lesion of the tubules leading to a prolonged state of oliguria or anuria even when the initial insult has been rectified on the initial depletion corrected. In the other state, acute oliguria or anuria may supervene, but it is completely correctible when the initial stress has been removed. I wish to confine my remarks to salt depletion. When a patient has had a profound restriction of salt for one reason or another, and has had a major surgical procedure, some period of oliguria or anuria frequently may develop. At times this may be severe. Under these circumstances it is often impossible to say whether or not the patient has suffered significant renal injury. The only way to be certain is to replace what is assumed to be a deficit and await the response. No convenient methods now are available for the measurement of extra cellular volume. The estimation of the deficity must rest on an intelligent appraisal of the clinical condition of the patient and a critical assay of the history that has preceded the period of anuria. It is my belief that it is slightly safer to overestimate the amount of salt and water to be replaced than to underestimate it. Nobody advocates flooding the patient and inducing massive edema. It is simply a question of restoring the volume of extracellular fluids to nearly normal volumes. During the course of lower nephron nephrosis, severe losses of salt and water may take place. This may occur in the form of diarrhea with ulcerative lesions of the colon. It may occur in mercury poisoning with severe diarrhea or it may occur if suction is employed to relieve ileus. Large amounts of salt and water are removed from the gastrointestinal tract in these instances. This can result

in a serious fall in renal plasma flow with delay in or prevention of restoration of renal function.

Moreover, the transport of sodium and chloride into the cells does not mean that the extracellular volume is normal. It means that the extracellular space is shrunken. The presence of sodium and chloride in cells doesn't necessarily immunize the body to the effect of depletion of salt. Under these circumstances, it is my view that it is safer to try to maintain the volume of the extracellular fluids at nearly normal values. I would, therefore, disagree with the position that small amounts of saline or bicarbonate are harmful, particularly if they are intelligently administered with a view toward maintaining the composition and volume of the extracellular fluid in a fairly normal manner.

QUESTION: Dr. Darrow, would you like to comment on this problem of salt depletion?

DR. DARROW: I was not aware that renal damage could be produced by a decrease in the circulation of the kidneys as a result of salt loss. It is possible that most examples of so-called lower nephron nephrosis accompany other types of shock rather than that which is associated with depletion of salt. I don't think Dr. Heller made himself absolutely clear; I understood him to say that at the start of treating anuria he corrected extracellular fluids to more or less what he thought was a normal volume and then started from there, using minimal amounts of salt.

QUESTION: Dr. Heller, can you explain this?

DR. HELLER: I started my talk by saying that in order to combat shock the patient who presents himself with profound electrolyte and fluid disturbances should be brought to a state of balance and then be observed carefully to see whether acute renal insufficiency is going to develop. As to depletion of salt, *per se*, causing the oliguric or anuric syndrome, the evidence is indeed to the contrary. The experiment done by nature in Addison's disease, in which a profound depletion of salt and water occurs, is not followed by anuria or oliguria. Some of the studies in England on salt and water depletion indicate a decrease in renal function, though it is not pronounced. There are no patients in my experience who have died in acute renal insufficiency or dehydration or depletion of the extracellular volume. The invariable finding at necropsy is pulmonary edema, and I think it is well established that these patients are extremely sensitive to replacement of salt and water. They have a tendency to experience pulmonary edema when even small amounts of salt and water are replaced.

To be sure it is desirable to have normal extracellular fluid volume, but it is completely undesirable to have patients dead of pulmonary edema with a normal volume of extracellular fluid. I would also re-emphasize that the spectrum of acute renal insufficiency is broad, in that some patients cannot be fitted into this particular category. I have mentioned the fact that patients who have depletion of salt and water may undergo some impairment of renal function but do not appear to fit exactly into the category of acute renal insufficiency. I agree with Dr. Darrow that acute renal insufficiency rarely follows depletion of water and electrolytes, *per se*, and that is why I divided the etiologic agents into shock, chemical toxins and hemolytic disorders.

Physiologic saline is decidedly unphysiologic in that it is hypertonic with regard to chloride and slightly high in sodium. The losses of electrolytes associated with fulminating diarrhea can be replaced quantitatively but with caution. However, the uncomplicated cases, with nausea and small amounts of emesis and diarrhea, are usually no problem, and I would not replace the salt and water in those instances.

If one becomes too eager in an attempt to replace the losses of serum sodium and chloride, the efforts may eventuate in pulmonary edema, since it takes such a small amount of fluid to precipitate pulmonary edema.

QUESTION: Dr. Lowe, if one chooses the sodium content of colostrum as representing the normal intake of sodium in an infant, can you give less than this normal amount after operation on the basis that you might anticipate some retention of sodium associated with the stress response. Secondly, please discuss your two polyionic solutions and their availability.

DR. LOWE: Dilute solutions that have a concentration of electrolytes somewhere in the range of colostrum would be acceptable for replacement fluid for a newborn child who requires an operation. With the use of such solutions, in more than 100 babies we have never seen postoperative edema. We have seen it in newborn babies, however, when we have used solutions that contain 40 to 60 mEq. per liter. It is my impression, and I think there is experimental evidence to substantiate it, that the newborn infant is extremely capable in handling water and is able to control both retention and excretion of electrolytes.

The solution that we call "Polyionic Solution No. 2" is now on the market and is manufactured by Baxter Laboratories. The other solution mentioned, also prepared for us by Baxter Laboratories, is not yet commercially available.

QUESTION: Dr. Sprague, would you discuss the use of specific alkali substances in the treatment of diabetic acidosis?

DR. SPRAGUE: We have not been in the habit of administering solutions of sodium bicarbonate or sodium lactate, *per se*. We have been using solutions that contain an excess of sodium over chloride. There are occasional instances in which early in the treatment of acidosis it is desirable to correct an acidosis rapidly in order to relieve hypertonia. This may occur in patients with severe diabetic acidosis that has been precipitated by a myocardial infarction. They experience air hunger even when lying in bed. In these patients it has been rather urgent to correct the acidosis as promptly as possible, and solutions of sodium bicarbonate have been administered with rapid benefit.

Classified Advertising

Replies to advertisements with key numbers should be mailed in care of MINNESOTA MEDICINE, *2642 University Avenue, Saint Paul 14, Minnesota.*

WANTED—General practitioner for State Hospital. Beginning salary $640.00 per month. Three bedroom house available, partially furnished, subsistence, garage. Government working conditions, paid holidays, vacation, sick leave, and retirement pension plan. Write Superintendent, Fergus Falls State Hospital, Fergus Falls, Minnesota.

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LOCATION AVAILABLE—Established medical location in Appleton, Wisconsin. Uptown business district, over prescription drug store. Six-room suite, large enough for two doctors. Will completely remodel. Rental $75.00 per month. Write or phone collect: B. E. Schwandt, Schlintz Drug Store, Appleton, Wisconsin. Phone 3-5645.

WANTED—Locum tenens for general practice February and/or March, 1956. General hospital. Write E-498, care of MINNESOTA MEDICINE.

FOR RENT—Established medical suite, ground floor, modern air-conditioned building; 1100 square feet plus reception room. Best Minneapolis North Side location. Write Dr. W. P. Marxen, 2014 Emerson Avenue North, Minneapolis 11, Minnesota. Telephone CHerry 5306.

FOR SALE—Large Minnesota EENT practice (mostly eye), long established, big territory, little competition. Reasonable. Retiring. Address E-503, care MINNESOTA MEDICINE.

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PLACEMENT SERVICE

The Minnesota State Medical Association maintains a Medical Placement Service for the benefit of physicians who are looking for locations and positions; also for communities, medical groups and physicians who are looking for licensed medical assistance. For information, write to the Minnesota State Medical Association, 496 Lowry Medical Arts Bldg., Saint Paul 2, Minnesota.

DOCTOR OR DENTIST—Beautiful suite in South Minneapolis. Very modern. Six months free rent. Then option of lease at very reasonable rent. Wm. L. Cochrane, 4101 - 42nd Avenue South, Minneapolis, Minnesota. Telephone Ro 9-8758.

FOR RENT—New 4-room, first floor office in fast-growing Minneapolis suburb of about 4,000. Private front and rear entrances. Adequate parking space. Telephone: WE 8-9660.

FOR RENT—Highland Shopping Area, equipped office available, full or part time. Share with surgeon and dentist. Excellent for general practice, obstetrics, pediatrics. H. Schwyzer, M.D., 2069 Ford Parkway, Saint Paul. Telephone: MI 8-4832 or CA 4-7416.

ATTENTION DENTISTS AND DOCTORS—Modern space available for dentists' and doctors' offices. A location where several sets of doctors and dentists have been long established and then built their own clinics. A money maker. Above Kisch's Food Market. Plenty of auto parking space. Apply 637 Stryker Avenue, Saint Paul, Minnesota.

FOR SALE—Picker Century 100 M.A., eight years old. Price includes developing tanks, cassettes and film cabinet—$1,450.00. Address R. E. Currie, M.D., Spooner, Wisconsin.

VACANCIES—Positions available for clinical directors, Boarded or Board-eligible, in the Mental Hospital System of the State of Minnesota, $799-879 per month. One tuberculosis specialist interested in psychiatry, $774-854 per month. Two psychiatrist positions $699-779 per month. Two physicians $626-696 per month. Direct reply to Dale C. Cameron, M.D., Medical Director, State Department of Public Welfare, 117 University Avenue, Saint Paul 1, Minnesota, giving full information about training and experience.

YOUNG GENERAL PRACTITIONER presently practicing in small town desires to relocate—prefers to associate with established doctor or group in city over 10,000 population. Address E-502, care MINNESOTA MEDICINE.

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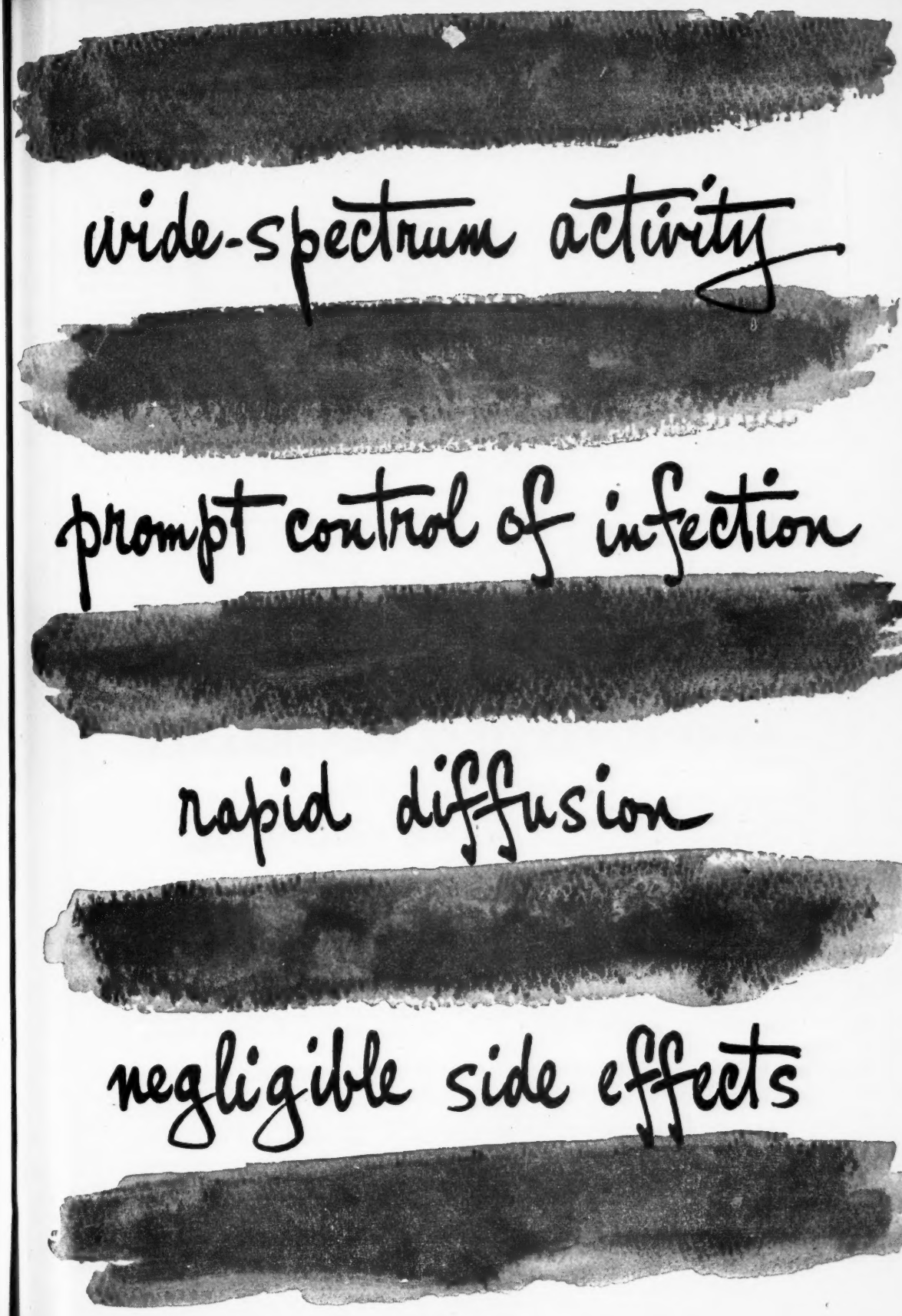
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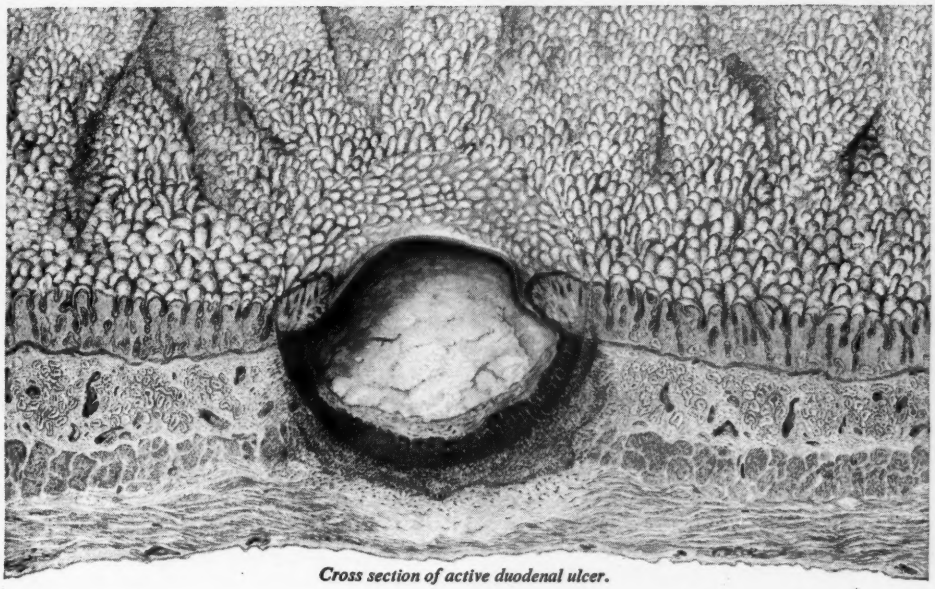

Cross section of active duodenal ulcer.

Dramatic Remission of Ulcer Pain

Pain of ulcer is associated with hypermotility; the pain is relieved when abnormal motility is controlled by Pro-Banthīne.

"In studying[1] the mechanism of ulcer pain, it is obvious that there are at least two factors which must be considered: namely, hydrochloric acid and motility.

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Pro-Banthine Bromide (β-diisopropylaminoethyl xanthene-9-carboxylate methobromide, brand of propantheline bromide) is a new, improved, well tolerated anticholinergic agent which consistently reduces hypermotility of the stomach and intestinal tract. In peptic ulcer therapy[2] Pro-Banthine has brought about dramatic remissions, based on roentgenologic evidence. Concurrently there is a reduction of pain, or in many instances, the pain and discomfort disappear early in the program of therapy.

One of the typical cases cited by the authors[2] is that of a male patient who refused surgery despite the presence of a huge crater in the duodenal bulb.

"This ulcer crater was unusually large, yet on 30 mg. doses of Pro-Banthine [q.i.d.] his symptoms were relieved in 48 hours and a most dramatic diminution in the size of the crater was evident within 12 days."

Pro-Banthine is proving equally effective in the relief of hypermotility of the large and small bowel, certain forms of pylorospasm, pancreatitis and ureteral and bladder spasm. G. D. Searle & Co., Research in the Service of Medicine.

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1. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, Gastroenterology *23*:252 (Feb.) 1953.

2. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, Gastroenterology *25*:416 (Nov.) 1953.

SEARLE

(Continued from Page 954)

Pueblo, Colorado, first vice president, and **Dr. James F. Weir,** Rochester, second vice president. **Dr. Donald C. Balfour** and **Dr. George B. Logan,** both of Rochester, were re-named honorary president and secretary-treasurer, respectively.

NEW LOCATIONS

Dr. A. M. Scheidel, who recently completed a three-year fellowship in internal medicine at the Mayo Clinic, has become associated in practice with Dr. B. R. Geurs and Dr. R. H. Conley in Mankato.

Dr. Robert L. Radke, formerly with the Yankton Indian Hospital, Wagner, South Dakota, is now affiliated with the Cass Lake Indian Hospital, Cass Lake.

Dr. E. E. Ulrich, formerly of Carey, Ohio, has become associated in practice with Dr. C. G. Wingquist and Dr. D. R. Nichols at Crosby.

HOSPITAL NEWS

Election of officers highlighted the annual meeting of the medical staff of the Waconia Community Hospital, Waconia, October 18. Named as chief-of-staff was **Dr. K. B. Romness,** Mound. Other officers elected include **Dr. R. S. Johnson,** Excelsior, vice chief-of-staff, and **Dr. Iwan Sawaryniuk,** Waconia, secretary.

MINNESOTA BLUE SHIELD-BLUE CROSS

On March 1, 1950, Blue Shield had 292,455 participant subscribers, while on September 30, 1955, 713,515 persons were enrolled in Blue Shield. During the month of February, 1950, 3,322 Blue Shield claims were paid, whereas, during September, 1955, 12,231 claims were paid. These figures show that there has been more than a two-fold increase in the number of subscribers, and more than a three-fold increase in the number of claims paid which constitutes the work-load.

During this same period, the number of Blue Shield employes has increased from 21 to 34. Most important of these increases is that involving claims auditors or examiners who have increased in number from three to eight. This increase in the number of claims examiners has been disproportionately small as compared with the increased number of claims. Two of the additional claims examiners are registered nurses increasing to three the number of nurses now processing claims.

In 1953 a professional relations program was initiated. Currently three members of this staff are engaged in calling upon doctors and their office personnel throughout the state. Besides keeping the medical profession informed regarding Blue Shield, the professional relations staff assists doctors' secretaries, nurses and receptionists in handling Blue Shield claims.

Along with the increases in activities, work, and personnel have come improvements in efficiency directed toward prompt payment of claims, more rapid handling of correspondence, more accurate telephone information and wider dissemination of information about Blue Shield in the medical profession.

According to figures just released from the statistical department of the Minnesota Hospital Service Association (Blue Cross), patients are staying in the hospital for slightly longer periods in 1954 than during 1955.

During the first nine months of 1955, 766,037.8 days of hospital care were provided for 124,949 Blue Cross subscribers compared to 751,778.2 days for 125,602 subscribers during the same period of the previous year.

Though there was a decrease of 653 cases in the first nine months of 1955 over the same period in 1954, days of patient care increased to 14,259.6.

The average length of hospital stay increased from 6.0 days in the first nine months of 1954, to 6.1 days during the same period of 1955.

Pregnancy care represented 17.1 per cent or 21,338 cases of all hospital care during the first nine months of 1955, compared to 21,166 cases or 16.9 per cent of care during the same period of 1954.

Accident cases accounted for the second largest segment of hospital cases. There were 19,574 accident cases representing 15.7 per cent of total cases paid during 1955 compared to 19,356 cases or 15.4 per cent of total cases paid during the same period of 1954.

Ranked as the fourth largest segment in 1954, digestive illnesses rose to third in 1955. There were 17,277 such cases during the first nine months of 1955, accounting for 13.8 per cent of all cases as compared to 16,819 cases or 13.4 per cent of the total for the same period in 1954.

Respiratory illnesses dropped from third place in 1954 to fourth place in 1955. There were 13,977 cases or 11.2 per cent of the total for the first nine months of 1955, as compared to 17,256 cases or 13.7 per cent in 1954.

Surgical, tonsillectomies and adenoidectomies seem to have accounted for the decrease. During the first nine months of 1955, there were 4,774 tonsillectomies, as compared to 7,344 such operations during the same period of 1954.

In comparing benefits paid, digestive illnesses seem to be the most costly. Hospital benefits for such care during the first nine months of 1955 exceeded $2,600,000. Pregnancy benefits amounted to $2,300,000. Diseases of the circulatory system ranked third in benefits paid, amounting to approximately $1,800,000 for the same nine-month period.

During the first nine months of 1955, Blue Cross cases and days in relation to number of effective contracts show a decrease of eight cases per year per 1,000 contracts, and an increase of 15 days per year per contract. This fact is reflected by the 0.1 day increase in length of stay compared to the same nine-month period of 1954.

Book Reviews

Books listed here become the property of the Ramsey, Hennepin and St. Louis County Medical Libraries when reviewed. Members, however, are urged to write reviews of any or every recent book which may be of interest to physicians.

SYNOPSIS OF PATHOLOGY. By W. A. D. Anderson. 3rd ed. 788 pages Illus. Price. $8.00. St. Louis: C. V. Mosby Co., 1952.

This book is truly a condensed pathology book. It fills a need for a rapid review of the important points of pathology. This form would be suitable for those physicians who have set up a comprehensive reading program to review the fields of basic medical sciences.

DONALD W. KOZA, M.D.

SEVENTY-FIVE YEARS OF MEDICAL PROGRESS, 1878-1953. Edited and with a foreword by Louis H. Bauer, M.D., F.A.C.P., Secretary-General of the World Medical Association, Past President of the American Medical Association. 286 pages. Illus. Price, $4.00. Philadelphia: Lea & Febiger, 1954.

The First Western Hemisphere Conference of the World Medical Association was held in Richmond, Va., in April, 1953. "Seventy-five Years of Medical Progress" was the theme of the conference. This book is a compilation of the papers presented by men who are among the outstanding in their specialties.

A period of seventy-five years was chosen because it was felt that during these years more has been learned about disease and its treatment than during the previous three thousand years. That is a startling claim, but as you read these papers you can begin to see the justification for such a claim.

The nineteen specialties chosen were the specialties as defined by the Advisory Board for Medical Specialties. In addition, general practice was also represented. Among the contributors, to name but about a fourth of them, are M. B. Sulzberger, N. J. Eastman, U. R. Bryner, J. S. Simmons, A. Blalock, and M. E. DeBakey.

It is exciting to read of the rapid advances made in each field. Besides the great achievements of this era being listed, broad trends are sometimes set forth; outstanding pioneers are given recognition; specific papers, or books, which have opened new vistas are occasionally cited. Each contributor, or team of contributors, has presented his specialty in the way he feels best depicts its progress. The interdependence of the various specialties is made clear to the reader as he sees how a discovery in one field opens new avenues of progress in another.

The book is a good summary of medical progress since 1878.

M.P.

MEDICAL SUPPORT OF THE ARMY AIR FORCE IN WORLD WAR II. By Mae Mills Link, Ph.D., and Hubert A. Coleman, Ph.D., with a foreword by Maj. Gen. Dan C. Ogle, Surgeon General, United States Air Force. Price, $7.00. Washington 25, D. C.: Government Printing Office, 1955.

This book, which required over ten years to compile, write, edit and print, tells how military medicine was

propelled into a new dimension as it became airborne. It contains valuable reading for military and civilian planners concerned with manpower, and every doctor will gain new insight into how the talents of the medical profession are forged into the iron framework of command to meet a national emergency. At the same time, the volume is interesting general reading because the human element is never lost.

Each chapter is thoroughly documented, with footnotes at the end of every chapter for easy reference. The volume is well illustrated with charts, diagrams, and photographs and includes extensive tabular data. There is a detailed index.

MANUSCRIPTS COLLECTIONS OF THE MINNESOTA HISTORICAL SOCIETY. Compiled by Lucile M. Kane and Kathryn A. Johnson. 212 pages. Price, $3.60. Saint Paul: Minnesota Historical Society, 1955.

A second guide to the Minnesota Historical Society's collection of four million manuscripts has just been issued. *Manuscripts Collections of the Minnesota Historical Society,* compiled by Lucile M. Kane and Kathryn A. Johnson, is a supplement to *Guide to the Personal Papers of the Minnesota Historical Society,* compiled by Grace Lee Nute and Gertrude Ackermann and issued in 1935. Together, these guides describe 1,645 groups of papers collected by the Society since its establishment in 1849.

Most of the manuscripts deal with Minnesota and with its many relationships with the other states in the Union. Several groups of papers that document the westward movement of a family from the east coast to the west are good examples of the national character of this "regional collection."

A thirty-seven-page index is the key that unlocks the wealth of material found in the volume.

REVISED SOUND FILM AVAILABLE

A completely revised, sound version of the film, "Development of the Gastro-Intestinal Tract," has just been released by The Center for Mass Communication of Columbia University Press. The 35-minute film, in color, was produced by Joseph J. McDonald, M.D., Professor of Clinical Surgery at the College of Physicians, Columbia University, and at present Dean of the Medical Faculty at the American University of Beirut, Lebanon.

The film depicts not only the embryology of the tract but also associated features such as the implantation of the ovum, the development of the placenta and early circulatory system as well as other structures closely related to the gastro-intestinal tract such as the body cavities, the main vessels and the diaphragm. It will be useful as an adjunct to the teaching of gross anatomy as well as to abdominal surgery and is most appropriate for showing to students of embryology and anatomy on both the graduate and undergraduate level.

Prints in 16mm for use by medical schools are available either for rental or purchase exclusively from The Center for Mass Communication, of Columbia University Press, New York 25, New York.

Announcing

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of

THE NEW ORLEANS GRADUATE MEDICAL ASSEMBLY

Conference Headquarters—Municipal Auditorium

FEBRUARY 27, 28, 29 and MARCH 1, 1956

GUEST SPEAKERS

Philip D. Woodbridge, M.D., Greenfield, Mass., **Anesthesiology**

J. Lowry Miller, M.D., New York, N. Y., **Dermatology**

Franz J. Ingelfinger, M.D., Boston, Mass., **Gastroenterology**

John I. Brewer, M.D., Chicago, Ill., **Gynecology**

S. Gilbert Blount, Jr., M.D., Denver, Colo., **Internal Medicine**

Eugene A. Stead, Jr., M.D., Durham, N. C., **Internal Medicine**

John H. Talbott, M.D., Buffalo, N. Y., **Internal Medicine**

Lawrence S. Kubie, M.D., New York, N. Y., **Neuropsychiatry**

Duncan E. Reid, M.D., Boston, Mass., **Obstetrics**

Frank W. Newell, M.D., Chicago, Ill., **Ophthalmology**

Claude N. Lambert, M.D., Chicago, Ill., **Orthopedic Surgery**

A. C. Hilding, M.D., Duluth, Minn., **Otolaryngology**

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THE POSTCLINICAL TOUR TO THE WEST INDIES AND CENTRAL AMERICA BY PLANE

Departure from New Orleans, March 2

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CORPS EXAMINATIONS FOR MEDICAL OFFICERS USPHS

A competitive examination for appointment of Medical Officers to the Regular Corps of the United States Public Health Service will be held in various places throughout the country on March 20, 21, and 22, 1956.

Appointments provide opportunities for career service in clinical medicine, research, and public health. They will be made in the ranks of Assistant and Senior Assistant, equivalent to Navy ranks of Lieutenant (j.g.) and Lieutenant.

Entrance pay for an Assistant Surgeon with dependents is $6,017 per year; for Senior Assistant Surgeon with dependents, $6,918. Qualified officers are promoted at regular intervals.

Benefits other than promotions include periodic pay increases, 30 days' annual leave, sick leave, medical care, disability retirement pay, regular retirement pay which is three-fourths of annual basic pay at time of retirement, and other privileges.

Active duty as a Public Health Service officer fulfills the obligations of Selective Service.

Requirements for both ranks are U. S. citizenship, age of at least twenty-one years, and graduation from a recognized school of medicine. For the rank of Assistant Surgeon, at least seven years of collegiate and professional training and appropriate experience are needed. For Senior Assistant Surgeon, an additional three years, for a total of at least ten years of collegiate and professional training and appropriate experience, are required.

Entrance examinations will include an oral interview, physical examination, and comprehensive objective examinations in the professional field.

Application forms may be obtained from the Chief, Division of Personnel, Public Health Service, Department of Health, Education, and Welfare, Washington 25, D. C. Completed application forms must be received in the Division of Personnel *no later than February 10, 1956.*

NORTHWESTERN UNIVERSITY REPORTS ON NEW GERMICIDE

Inflammation of the bladder apparently can be treated successfully with a new germicide, it is reported in the *Quarterly Bulletin of Northwestern University Medical School.*

The germicide, chlorpactin WCS-90, a derivative of chlorine, gave "dramatic improvement" to patients with painful cystitis, said Dr. Vincent J. O'Conor, chairman and professor of urology at the school.

The recently developed germicide solution was used in forty-eight patients who for many years had inflammation of the bladder and painful, frequent urination which could not be eradicated by drugs. With chlorpactin, "spectacular improvement was achieved" in nearly all the patients, said Dr. O'Conor.

The exact cause of the bladder inflammation, called chronic interstitial cystitis, is not known. The capacity of the bladder gets smaller and smaller, so urination is frequent and painful. The condition is 30 times more prevalent in women than in men.

Dr. O'Conor wrote that "one hesitates to recommend a new treatment for interstitial cystitis. This intractable condition has been a bugbear to urologists ever since Dr. Hunner of Baltimore described it in 1915. About every sort of treatment, both local and general, for increasing the capacity of the bladder in cases of elusive ulcer with interstitial cystitis has been used."

But he continued that "this treatment was applied to individuals who had been under our care for many years and who had never had a satisfactory improvement of anything but a very temporary nature. The results in the limited series of these very chronic and intractable cases have been so spectacular that it seems a further trial is warranted by the profession at large."

The new germicide also has been reported to be successful in preliminary trials for treating tuberculosis of the bladder and diseases of the mouth, for sterilizing instruments, and as an antiseptic for surgery. When the powder form is added to cool or lukewarm water, it results in liberation of hydrochlorous acid.

"It is said," wrote Dr. O'Conor, "that even the concentrated powder is not harmful to normal tissues."

In the preliminary trials with chlorpactin, a weak solution of the germicide was used to stretch the bladder. Usually after the first treatment, the condition became worse, he said, but the temporary distress soon disappeared with subsequent "great and rapid improvement." The treatments were continued one or two times weekly for five treatments, then decreased to once a month or longer.

The trials with chlorpactin have only lasted seven months, but, wrote Dr. O'Conor, "the improvement obtained in these patients has been so dramatic that it prompts us to make this preliminary report in the hope of encouraging others to try a similar method of treatment."

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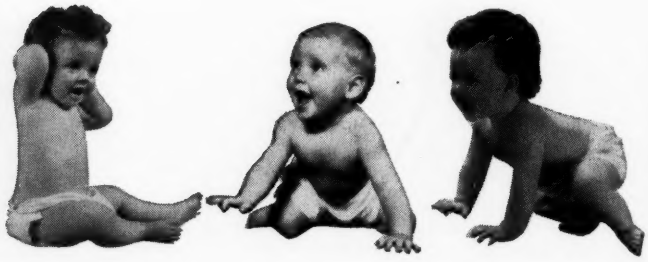

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(1) Jeans, P. C., in A. M. A. Handbook of Nutrition, ed. 2, Philadelphia, Blakiston, 1951, pp. 275-278.

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